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Functional Prepuberal Castration in Males[1]

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FROM the large and heterogenous group of adults with retardation or absence of sexual development two new clinical syndromes have been recently delineated. The first, which includes the association of short stature, retarded sexual development and high urinary gonadotropin titers in women, has been described by Varney, Kenyon and Koch (1), and by Albright, Smith and Fraser (2). The second syndrome represents seminiferous tubule failure accompanied by gynecomastia and high urinary gonadotropins in men and has been described by Klinefelter, Reifenstein and Albright (3). To these two syndromes we should like to add a third which has many features in common with the syndrome described by Kenyon, but occurs in males. In essence the syndrome may be regarded as a functional prepuberal castration.

The syndrome as observed by us in 6 cases was characterized by *a*) presence of Wolffian duct structures in the scrotum, but absence of functional testes. In 4 cases the scrotum seemed empty, suggesting the diagnosis of cryptorchidism, but biopsy demonstrated the presence of Wolffian duct structures. In 2 cases remnants of atrophic testes along with Wolffian duct structures, as confirmed by biopsy, were palpable in the scrotum. *b*) Infantilism, which was complete in the following features: high pitched voice; absence of hair on the body, extremities and face; female distribution of sparse pubic hair; infantile penis and scrotum; presence of erections, but absence of ejaculation; small undeveloped prostate gland. *c*) Stature was *not* excessively tall as in other types of eunuchoidism, but tended to be normal or short. *d*) Eunuchoidal skeleton in 4 cases. The span was greater than the height, lower measurements greater than upper. *e*) Moderate delay in osseous development, which included delay in formation and closure of epiphyses and

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small or rudimentary frontal sinuses. *f*) Gynecomastia was observed clinically in 3 cases while in all 6 cases biopsies of the breasts showed departures from the condition of the normal male mammary gland. *g*) High urinary titers of gonadotropic hormone. These were several times the normal level and were comparable to titers observed in male and female surgical castrates. Two constituents of the gonadotropic complex, *i.e.*, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were present in the urine. *h*) 17-ketosteroid excretion was either subnormal or in the lower range of normal. *i*) Urinary estrogens were subnormal or in the lower range of normal variation. *j*) There was no response to therapy with chorionic gonadotropins. *k*) Marked clinical improvement followed substitutional therapy with testosterone propionate. This response indicated that the end-organs were not refractory.

METHODS

The patients[3] ranged in age from 19 to 57 years and were in good health. The following studies were conducted in every case: biopsy of scrotal contents; biopsy of mammary gland; roentgen studies of skull, frontal sinuses and pelvis; assays of urinary gonadotropins, 17-ketosteroids and estrogens; blood levels of cholesterol; routine urinalyses; and complete blood counts. Basal conditions were not always attained because of long distances from home to hospital and irregular working hours of the patients, but in 4 cases satisfactory recordings indicated lowered oxygen consumption. These ranged from −3 to −13 per cent. Tissues obtained by scrotal and mammary biopsies were fixed in Bouin's solution and stained by Masson's trichrome method, hemotoxylin and eosin or iron hemotoxylin.

Urine collections for the hormonal assays were made during the 12-hour period which included the patient's sleeping and leisure hours. At least 5 separate specimens were collected to establish the pre-treatment levels of hormonal excretion. Each assay was performed on a separate urine specimen.

Urinary gonadotropins were concentrated by the alcohol precipitation dialysis, alcohol reprecipitation method of Heller and Chandler (4). Increases in ovarian and uterine weights of immature 22- to 24-day-old female rats were used as assay end-points as previously described by Heller, Lauson and Sevringhaus (5).

Suggestions made at the Conference on Ketosteroids called together by The Josiah Macy, Jr. Foundation (6) were incorporated in the procedures for assay of 17-ketosteroids. These were performed as follows: 100 cc. aliquots of urine were brought to pH 1.0 using HCl and were hydrolyzed for 20 to 30 minutes. Fifty cc. of hydrolyzed urine were extracted with CCl_4 by repeated shaking. Extracts were washed twice with 2 N NaOH followed by washing with 10 cc. of Lycopon (1 N NaOH, 100 cc.; sodium hydrosulphite, 10 gm.) to remove interfering chromogens. After washing with distilled water, the CCl_4 was removed by distillation. The remaining dry powder was dissolved in 100 per cent aldehyde-free ethyl alcohol. The Holtorff-Koch (7) aqueous alcohol modification of the Zimmermann reaction was employed. No color correction was made. This procedure results in a value of zero for children between ages of 2 and 3 years. Values for normal adult males range from 4 to 13 mg. equivalents of androsterone per 12-hour period. Reifenstein, *et al.*, (8) and Pincus (9) have demonstrated that collections made during the active waking hours contain more ketosteroids than similar 12-hour collections made overnight. Thus, in comparing our values on 12-hour collections with those obtained on 24-hour collections slightly more than double the 12-hour value must be used.

Urinary estrogens were extracted with chloroform for 4 to 6 hours, following 30 min. of hydrolysis at pH 1.0 using HCl, in a continuous Wolfe-Hirshberg extractor. Extracts were taken up in 3 cc. of peanut oil and $\frac{1}{4}$ of the 12-hour equivalent was injected into 23- to 24-day-old immature female rats as described by Lauson, Heller, Golden and Sevringhaus (10). Daily injections of 0.25 cc. were made for 3 days. At autopsy, on the 5th day, uterine weight and the condition of the vaginal introitus were recorded.

RESULTS

Clinical features along with the essential laboratory results are recorded in table 1. The results of blood cholesterol determinations, complete blood counts and urinalyses are not tabulated since these were within the limits of normal variation.

[3] All cases, except *case 1*, were contacted at the Detroit Armed Forces Induction Center, through the courtesy of Lt. Col. Roscoe Cavell and the special clinical vigilance of Capt. L. G. Bateman and Capt. M. B. Sofen.

TABLE 1. CLINICAL FEATURES OF 6 CASES OF FUNCTIONAL PREPUBERAL CASTRATION IN MALES

Case No.	1	2	3	4	5	6
Age, yr.	57	35	24	21	24	19
Weight, lb.	126	190	160	222	130	114
Height, in.	58.75	67.5	68.5	70.75	69.25	67.62
Height of Relatives, in. (Males)	64 72	aver. 68	66 71 70.5 73	68.5 74	63 65	68.5 76 70.5
Span, in.	61.5	68.25	76	72.75	71	70.75
Sole to Sym. Pub., in.	29	34	37	37.5	37	37.5
Pub. Sym. to Vertex, in.	29.75	33.5	31.5	33.25	32.25	30.12
Voice Pitch	high	high	high	high	high	high
Recession Scalp Hair	slight	slight	none	none	none	slight
Facial Hair	none	none	none	none	none	none
Axillary Hair	very sparse	very few	very sparse	few	few	very few
Pubic Hair	sparse	sparse	sparse	sparse	sparse	sparse
Body Hair	none	none	none	none	none	none
Hair, Extremities	none	none	none	slight, forearms and legs	none	none
Duration Gross Gynecomastia, yr.	>20	17	none	8	none	none
Penis Length, in.	1	1.5	infantile before R	1.5	infantile before R	1.5
Erection	at will	at will	at will	at will	at will	at will
Ejaculation	none	none	none	none	none	none
Testis Size, Gross	navy bean	pea	none	none	none	none
Testis, Microscopic	atrophic	atrophic	none	none	none	none
Wolffian Duct Structures	present	present	present	present	present	present
Prostate	normal shape; ½ size	scarcely palpable; only thickening of area	norm. size and configuration after R	norm. shape ½ norm. size after R	palpable only as thickened area	normal configuration; about ⅛ normal size
Iliac Crests	present open to closed	fused	present; open 1–2 mm.	present open 1–3 mm.	present open 0–3 mm.	absent

Case 1, age 57 years (fig. 1) had what appeared, upon clinical examination, to be navy bean-sized testes in the scrotum. Biopsy of the mass on the left side of the scrotum revealed only an undifferentiated connective tissue mass and a few loops of vas deferens. A second operation was performed and the entire contents of the right scrotum were removed. This mass, which was surrounded by fatty tissue, grossly appeared to be spermatic cord, epididymis and testis (fig. 7). Serial section of the mass confirmed the impression that a small but otherwise normal spermatic cord and epididymis were present, but the region of the mass identified as testis showed a condition of almost complete atrophy. The major portion of the testis was made up of collagenous fibers with scattered hyalinized areas. These had the gen-

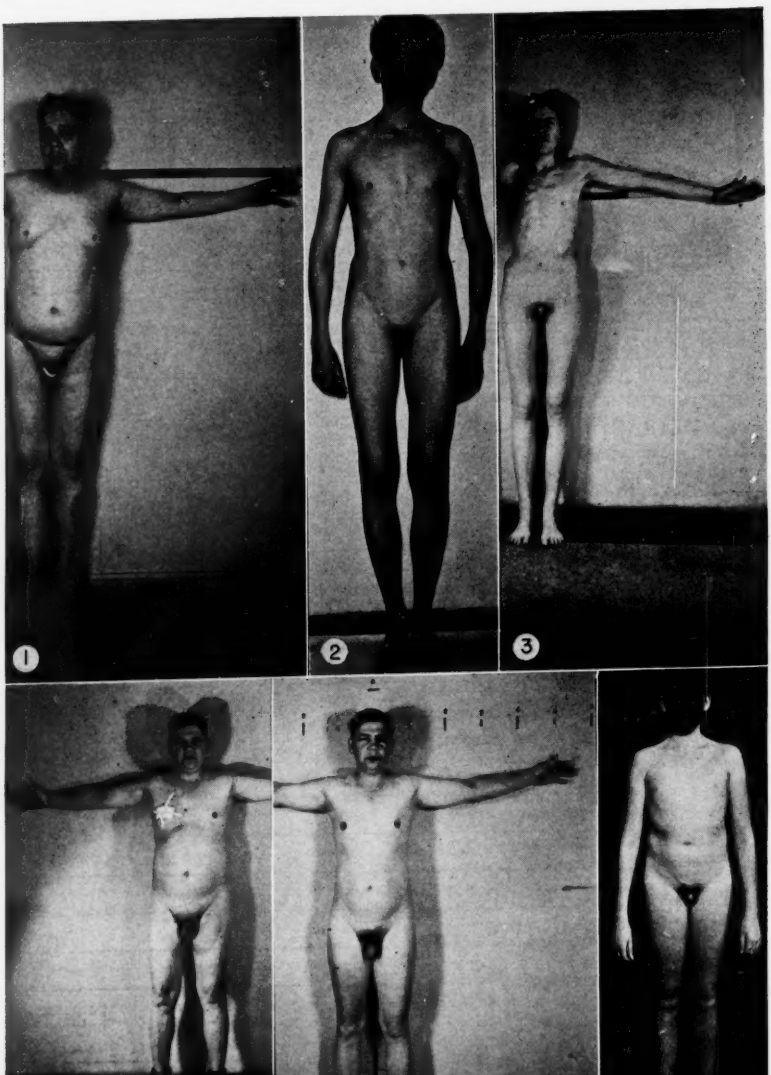

FIG. 1. *Case 1*, age 57 years. Note gynecomastia and short stature.
FIG. 2. *Case 5*.
FIG. 3. *Case 6*.
FIG. 4. *Case 2*, before therapy. Hematoma of right side of scrotum followed biopsy procedure.
FIG. 5. *Case 2*, after treatment with testosterone propionate given in 25 mg. amounts intramuscularly 5 times weekly for a total of 75 injections.
FIG. 6. *Case 3*, at age 19 after a minimal amount of treatment. Picture courtesy of Dr. Robert L. Schaefer.

eral shape of seminiferous tubules, but lacked epithelial constituents (fig. 8). No cells of Leydig could be identified. In the mediastinal area a patch of collapsed rete tubules was present and a few adjacent epithelial coils were regarded as efferent ductules. The tunica

albuginea was relatively very thick. In this case then there is conclusive evidence of complete atrophy of the testes. The fact that the history of this individual shows a lack of sexual development at any time suggests that his testes never had assumed normal puberal function and indicates that the defect almost certainly was present prepuberally.

Case 2, age 25 years (fig. 4) upon physical examination revealed what seemed to be pea-sized testes embedded in fatty tissue. A biopsy of the right side disclosed only a small coiled vas deferens in which the epithelium, lamina propria and muscularis were all fairly normal (fig. 11). Elements of a pampiniform plexus were present. After testosterone therapy (25 mg. of testosterone propionate daily 5 times a week for a total of 75 injections) almond-sized masses were evident bilaterally in the scrotum. Biopsy of the mass on the left side divulged a testicular structure which was essentially similar to that seen in *case 1*. Most of the specimen (fig. 12) showed only collagenous connective tissue with scattered patches of sclerotic seminiferous tubules. A minority of tubules contained Sertoli cells only while a few showed spermatogonia and spermatocytes. Two tubules contained a few spermatids. All of these tubules with epithelial elements were very small and presented a thickened and hyalinized tunica propria. Although a considerable number of intertubular cells were present, none of these could be identified as cells of Leydig by our routine histoligical methods or by special techniques (fat stains, polarizing microscope). It is probable that in the past the testes of this patient exhibited a better degree of development than at the present time.

Case 3, age 24 years, (fig. 6) had been under treatment off and on since age 17. An exploratory operation was performed in 1938 at another hospital for the purpose of locating the gonads. No testicular tissue was found in the right inguinal canal or within the abdomen. In May, 1943, after 100 injections of testosterone propionate (5 injections of 25 mg. each weekly for 20 consecutive weeks) had been given, a small indefinite mass was palpated in the left side of the scrotum. Biopsy of this mass disclosed nothing except the remnants of a structure which resembled a spermatic cord (fig. 13). Upon serial section this structure was seen to be composed of a mass of collagenous connective tissue. In one area a few small tubules identified as epididymis were present. Serial tracing showed that these tubules ended blindly but in the direction of their path a whorled arrangement of the connective tissue was suggestive of the stroma of a vas deferens. No lumen was present at any point. Along the path of this area a definite plexus of blood vessels and nerves was present. The only location left unexplored in this patient is the left inguinal canal, in which no masses could be detected by palpation.

Case 4, age 21 years (fig. 17), was diagnosed as being bilaterally cryptorchid and had a bilateral exploration of the inguinal canals in another hospital at age 14. No testes were located in the inguinal region or in the abdomen. At the initial examination in December, 1942, no masses were palpable in the scrotum and the latter appeared empty when a biopsy was performed at that time. However, after 50 injections of testosterone propionate (25 mg. daily 5 times weekly for 10 consecutive weeks) two scrotal masses the size of lima beans were discovered. Biopsy of the masses revealed a small yellowish bead of tissue attached to a cord on the left side while a cord only was present on the right side. Microscopic examination disclosed epididymis (fig. 14) and vas deferens on the left side, vas deferens only on the right side. The epithelial, muscular and connective tissue layers of these structures were well defined and normal in appearance

Case 5, age 24 years (fig. 2), first received medical attention in 1926 at age 5 when the diagnosis of bilateral undescended testes was made at another hospital. According to the record of the case the scrotum was empty, but two small masses could be felt in the pubic region. Both inguinal canals were explored and each presented " . . . hernial sac, containing very small testis and epididymis. Sac was cut away and testis lengthened by *ligating vessels of cord* . . . and neck of scrotum narrowed by suture, preventing the retraction of testis." Neither the parents nor the patient can recall any definite masses being present in the scrotum even after the operation. When the patient was first seen by us in 1942 only an in-

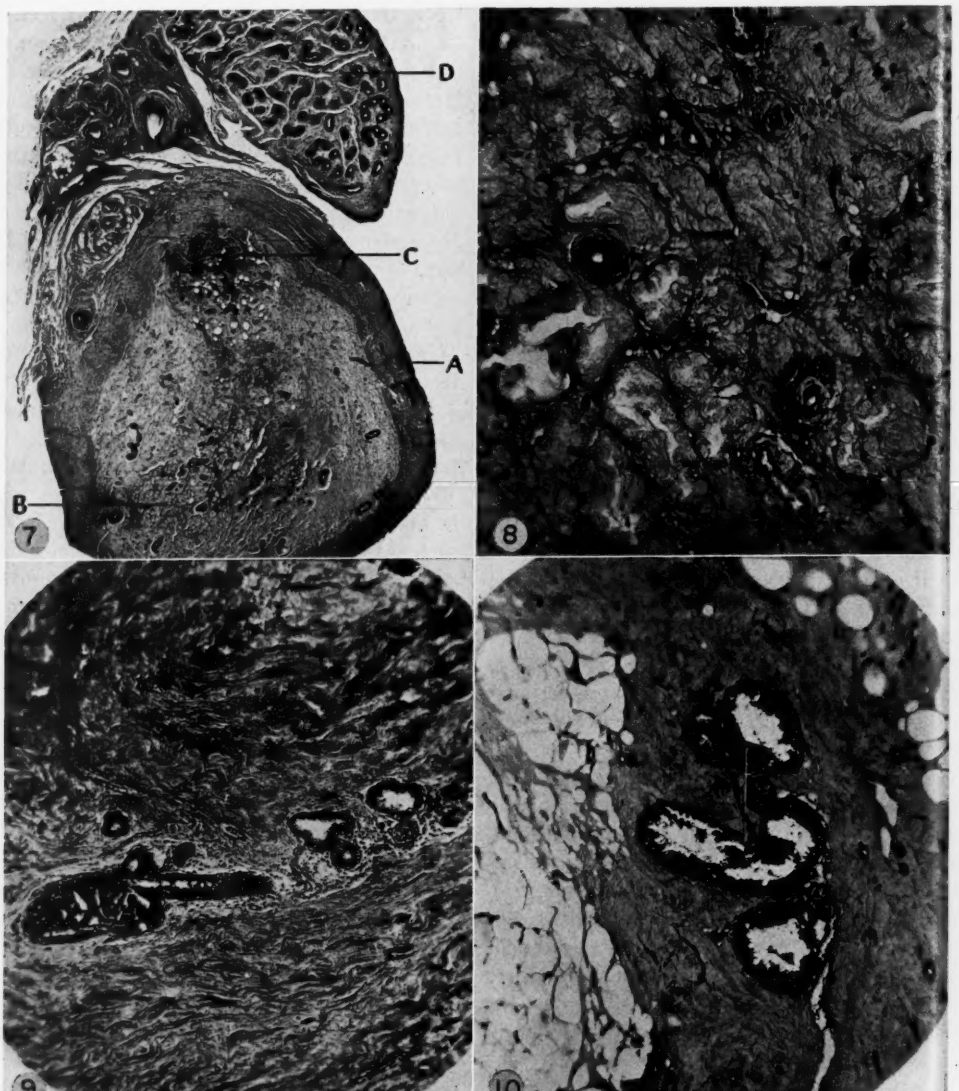

FIG. 7. *Case 1*, section through contents of right scrotum showing atrophic testis with A) thickened tunica albuginea, B) completely sclerosed seminiferous tubules, C) rete testis, and D) epididymis. ×6.

FIG. 8. *Case 1*, section through area of sclerosed seminiferous tubules. Note complete absence of epithelial elements and replacement by hyalinized collagenous connective tissue. Leydig cells are absent. ×175.

FIG. 9. *Case 2*, mammary biopsy, from a patient with gross gynecomastia, showing several ducts and one lobule with a group of alveolae. Note the dense interlobular connective tissue and the more loosely arranged intralobular connective tissue. ×100.

FIG. 10. *Case 3*, mammary biopsy, from a patient without gross gynecomastia, showing several ducts and no alveolae. Interlobular connective tissue is less extensive than shown in figure 9 and more extensive than normal. No intralobular connective tissue. ×125.

definite mass was palpable scrotally. Biopsy of the mass and serial section of the specimen divulged only fat and connective tissue. No testicular elements or Wolffian duct derivatives were identified. A course of treatment with testosterone propionate (25 mg. 5 times

weekly for 15 consecutive weeks) resulted in an enlargement of the scrotal mass and a second biopsy was performed. At this operation the contents of the scrotum again appeared to be principally fat and connective tissue, but a portion of the mass was suggestive of a small epididymis and vas deferens. Serial section confirmed this (fig. 15) and in addition revealed the presence of a group of efferent ductules which connected with the epididymis, but terminated blindly at their opposite ends. Although these various structures were smaller than normal, they were well-formed and showed evidence of having been stimulated by the treatment. The region of the mass which, on a topographical basis, should have been testis consisted of collagenous and mucoid connective tissue with a tangled net of blood vessels (fig. 15). No remnants of seminiferous tubules could be found and the architecture showed nothing to suggest that the mass might have been a testis at some earlier time. Although several small groups of epithelioid cells were scattered in various regions of the mass, they could not be identified with any degree of certainty as cells of Leydig. Neither did they closely resemble aberrant adrenal cortical tissue. In the light of the biopsy findings, two possibilities exist in explanation of the presence of Wolffian duct derivatives and the absence of testes. *a*) The latter may never have been present. However, the description of the operation at age 5 claimed the presence of testes. *b*) The ligation and section of the vessels of the cord, described in the case record, interfered with the vascular supply (internal spermatic artery) of the testes to such an extent that the latter underwent complete atrophy. This would not necessarily involve the epididymis and vas deferens if the artery of the vas deferens, a branch of the superior vesical artery, escaped section. This artery could adequately supply the epididymis as well as the vas deferens since it anastomoses with those branches of the internal spermatic which vascularize the epididymis. However, it is unlikely that this collateral circulation could be effective in preserving the testis and it seems reasonable to regard this patient as a castrate following the operation at age 5.

Case 6, age 19 years (fig. 3), had no palpable masses in the scrotum. Biopsy disclosed no Wolffian structures on the left side. On the right a small bead of yellowish tissue was attached to a cord-like formation found just below the external inguinal ring. The general arrangement of connective tissue fibers and smooth muscle in a whorl-like fashion accompanied by blood vessels and nerves as in a pampiniform plexus suggested that the mass was an atrophic vas deferens without lumen or epithelium (fig. 16).

In three cases (*1*, *2* and *4*) the breasts were enlarged. The hypertrophy was diffuse and not confined to the presence of sub-areolar nodes. None of the patients complained of pain and there was no evidence of mastitis. The gynecomastia had been present for periods ranging from 8 to 20 years. The relation of its onset to puberty is uncertain in all of the cases.

Biopsies of these breasts, when compared with preparations of normal male breasts, showed a significant increase in dense collagenous connective tissue (interlobar; interlobular connective tissue). The fibers were heavier and more closely packed and the tissue occupied an area appreciably greater than in the normal breast. In *cases 1* and *2* (fig. 9) numerous ducts of various sizes and several groups of end-buds or alveoli were observed. Although the number and size of ducts in these breasts were only slightly increased over the normal, the presence of end buds and alveoli, which are rarely observed in the normal male breast, must be regarded as significant. A more loosely arranged connective tissue, rich in cells and poor in fibers, was present around some of the smaller ducts and the alveoli. This type of stroma, usually designated as intralobular connective tissue, is commonly seen in the female breast, but we have encountered it in any quantity only exceptionally in our specimens of the normal male breast. This picture has been observed in cases of gynecomastia by Andrews and Kampmeier (23) and Geschickter (24). In *case 4*, ducts of various sizes were numerous, but no alveoli could be identified and only a scanty amount of intralobular connective tissue was seen. Biopsies were obtained in *cases 2* and *4* prior to treatment with androgen and in *case 1* after treatment had been initiated.

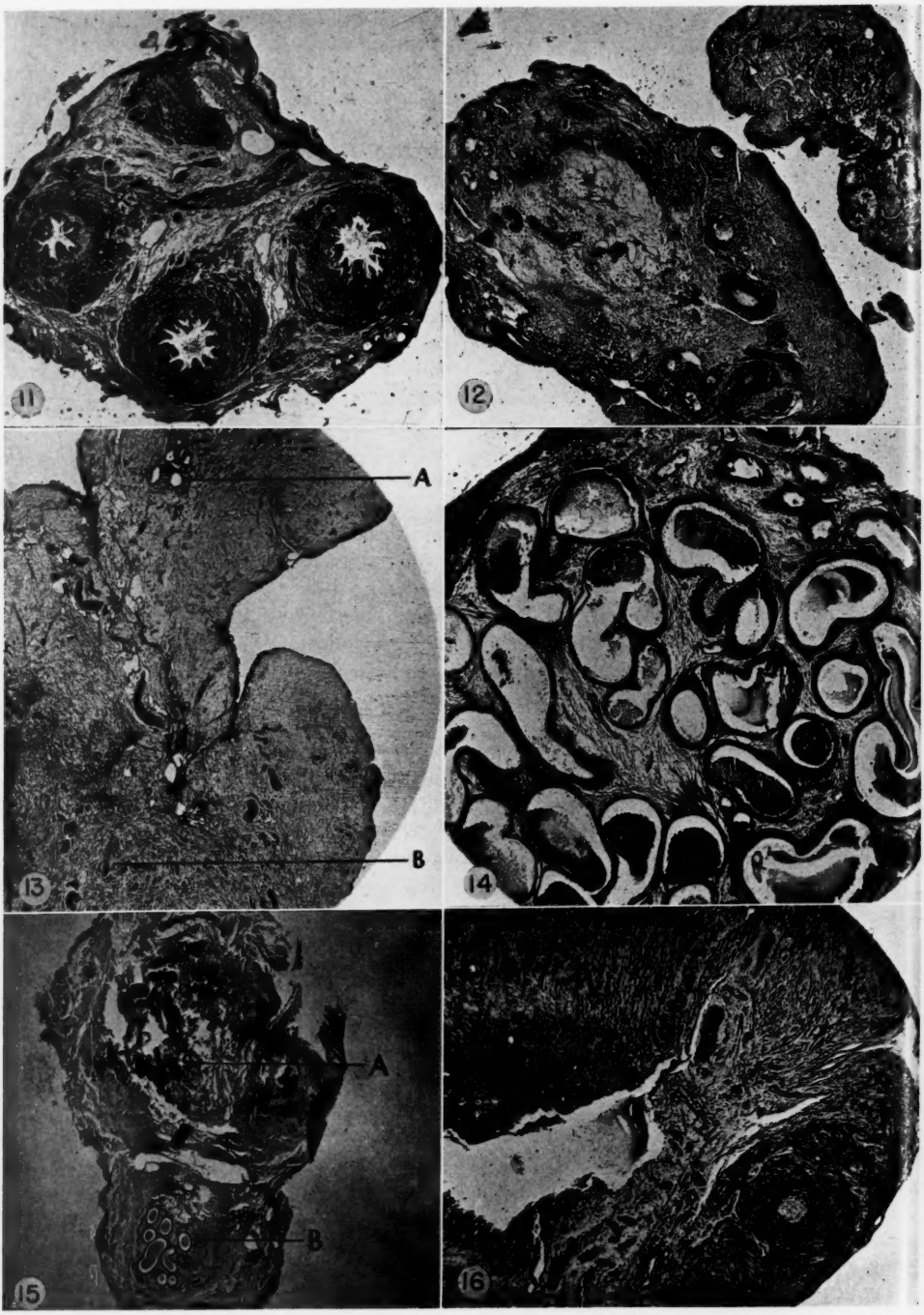

FIG. 11. *Case 2*, section through biopsy of right scrotal mass taken before therapy was instituted. Note coils of vas deferens. ×20.

FIG. 12. *Case 2*, section through biopsy of left scrotal mass after 75 injections of 25 mg. each of testosterone pro-

The remaining cases (*3*, *5* and *6*) showed no gross mammary hypertrophy. Biopsies were obtained before treatment in *case 6* and while treatment was in progress in *cases 3* and *5*. These each showed an increase in dense connective tissue similar to that noted for the patients who displayed grossly enlarged breasts except that it was less marked. Ducts of various sizes were numerous although it is probable that these were not increased significantly over the normal. No end-buds or alveoli were seen and only a scanty amount of intralobular connective tissue was present (fig. 10).

In summary, it may be said that the breasts of 3 of our patients showed gross enlargement while in 3 the breasts were normal in external appearance. In all cases an appreciable increase in dense connective tissue was present while in 3, those with gross gynecomastia, a slight increase in number of ducts, an occurrence of alveoli, and a significant increase in intralobular connective tissue were all observed. It would seem that we are dealing with a condition which may be regarded as a true gynecomastia in 3 of the patients while the increased amount of dense connective tissue in the remaining 3 is considered as a departure from the normal. It is noteworthy that the greatest degree of change was observed in the breasts of the older patients. This may indicate that the factors, whatever they may be, which were responsible for the gynecomastia in these patients had been active for a longer time in the older patients. Support for this possiblity may be gained from the fact that in our experience the breasts of some senile men show changes similar to those described for *cases 1* and *2*. Furthermore, Wagenseil (25) who studied a group of 31 Chinese eunuchs included illustrations of his subjects. Seven of these, all castrated during puberty or adolescence, showed gross gynecomastia when they were studied at ages ranging from 53 to 74 years.

In contrast to the small amount of gonadotropic hormones excreted by normal males (Heller, Heller & Sevringhaus, 11; Werner, 12) all 6 of our patients excreted large amounts. Since an entire 12-hour urine concentrate was injected into one immature female rat in this study, normal males were restudied using the same method. The response to urine concentrates from normal males was characterized occasionally by opening of the vagina, usually by evidence of uterine stimulation, and rarely by evidence of ovarian stimulation. Ovarian weights ranged from 7 to 16.2 mg. The response to urine concentrates from all 6 functional prepuberal castrates was characterized by constant vaginal opening, constant uterine stimulation, and constant ovarian stimulation. Average ovarian weights from 3 or more assays ranged from 57 to 151 mg. (see table 2).

Both follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were being excreted by these patients. The evidence for excretion of luteinizing hormone is: *a*) presence of corpora lutea or luteinized follicles; *b*) progestational uterine changes which are indicated grossly by the lack of intra-uterine fluid and thickening of the endometrium and myometrium. The increase in excretion of both follicle-stimulating and luteinizing hormone is compatible with the failure or absence of both seminiferous tubules and Leydig cells in these patients.

The excretion of 17-ketosteroids varied from 2.4 to 8 mg. equivalents of androsterone per 12-hour period and were higher than in the short women described by Albright, *et al.* In only one instance was the excretion distinctly below normal, 4 were considered as being low normals, and one as an average normal.

Determinations of urinary estrogen were

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pionate. Note that this represents atrophic testis. The smaller piece contains numerous completely sclerosed tubules with a few showing Sertoli cells and germinal elements. ×25.

FIG. 13. *Case 3*, section through scrotal mass taken after years of androgenic therapy. Note: A) coils of small epididymal tubules, B) whorl-like arrangement of connective tissue and blood vessels simulating vas deferens and pampiniform plexus. ×10.

FIG. 14. *Case 4*, section through left scrotal mass showing epididymis after intensive androgenic treatment. ×20.

FIG. 15. *Case 5*, section through biopsy of scrotal mass after 75 injections of 25 mg. each of testosterone propionate. Note: A) region regarded as atrophic testis, B) coils of epididymis. ×10.

FIG. 16. *Case 6*, section through scrotal mass, note whorl-like arrangement of connective tissue which represents stroma of an atrophic vas deferens. ×25.

made in every case. Neither before nor after treatment did estrogen levels exceed those of normal males or males with other forms of hypogonadism. Indeed, the excretion of estrogen was lower than normal in the untreated cases and rose to approximately normal levels during treatment with androgen. This rise in estrogen may represent metabolites of the administered androgen.

TABLE 2. DATA ON ASSAYS OF URINARY GONADOTROPINS, 17-KETOSTEROIDS AND ESTROGENS IN FUNCTIONAL PREPUBERAL CASTRATES

Patient No.	Testosterone Propionate Therapy[1] Duration	Gonadotropin Assays in Immature Female Rats					17-Ketosteroids		Estrogens	
		No. of assays	Uterine wt. with fluid	Uterine wt. without fluid	Ovarian wt.	Ovarian[2] development	No. of assays	Mg./12 hours[3]	No. of assays	Uterine wt.
	mo.		*mg.*	*mg.*	*mg.*					*mg.*
1	0	6	107	80	75	Luteinization	2	3.7	1	13
	2	3		17.5	9.7	Undeveloped	8	6.8	4	49
2	0	3	110	99	151	Luteinization	1	4.2	1	24.3
	2	4	236	96	45	Follicles only	1	11.8		
	3	3		17	13.7	Undeveloped	2	3.3		
3	0	4	114	114	107	Luteinization	1	5.1	2	27
	1	3	147	102	73	Luteinization	1	4.6		
	2	3	179	98	68	Follicles only				
	3	4	201	103	42	Follicles only			1	12.4
	5	4	166	95	28	Follicles only	1	4.7		
4	0	8	136	94	57	Luteinization	2	5.9	3	23.9
	1	3	118	89	74	Luteinization				
	2	3	223	94	33	Follicles only			4	29
	3	3	93	49	30	Follicles only	3	4.5		
	4	3	50	44	26	Follicles only				
	0						1	5.1		
5	0	3	172	86	95	Luteinization	3	7.2		
6	0	4	168	95	111	Luteinization	2	2.9	3	21.5
	1	1	250	109	36	Follicles only				
Normal Men	0	50	17–250	17–95	10–16	Undeveloped	15	4–13	5	26–69

[1] Testosterone propionate, 25 mg. daily, given 5 times weekly. Urines collected on 6th or 7th day of each week.
[2] Ovarian development means gross and transilluminated appearance of ovaries. Evidence for luteinization was not necessarily seen in every individual assay.
[3] Expressed as equivalents of androsterone.

Results of Treatment

Cases 3 and *5* had been given courses of therapy with chorionic gonadotropin by other physicians before the present study. This was reported to be without benefit.

All of the patients have been placed on treatment with testosterone propionate.[4] The general plan has been to administer 25 mg. daily 5 times weekly for 3 or 4 months and then to allow a rest period. The fact that response to this regimen has been uniformly excellent (fig. 4, 5, *case 2;* fig. 17, 18, *case 4*) signifies that the endorgans are not refractory. It further illustrates that response of the endorgans is possible even in instances in which therapy is begun late in life. Thus the 57-year-old patient responded as well as did the younger individuals.

Since the clinical response to testosterone has been described repeatedly, individual results will not be listed. The general order of response is interesting and may be summarized briefly as follows: the number of erections are increased within the 1st week of therapy; ejaculation usually occurs by the 3rd week, although the seminal fluid contains no spermatozoa; the voice changes in from 2 to 4 weeks.

[4] Testosterone propionate (Oreton) has been supplied us in most generous quantities through the courtesy of Mr. George Straayer and Dr. Max Gilbert of the Schering Corp., Bloomfield, N. J., for which we are deeply grateful.

The genitalia begin enlarging by the tenth day and continue to increase in size for many months. If Wolffian duct derivatives are present in the scrotum, these increase in size and often simulate small testes. The prostate gland increases to nearly normal size in 2 to 3 months. The obese individuals tend to lose and the thin ones to gain weight. In both thin and obese subjects definite evidence of increase in hair growth occurs in the following sequence: pubic, 2 to 4 weeks; lower arms and legs, 4 to 8 weeks; upper thighs and in line from pubic region to umbilicus, 3 to 4 months. Growth of axillary and body hair occurred in *case 3* who had intensive therapy during the past 3 to 4 years. No facial hair growth has occurred in these patients. In general, then, the order of response is somewhat similar to that which occurs during normal adolescence. The psychic effects are amazing, the entire personality changing from the anti-social to the gregarious. These have been described by Pratt (13) and others and need not be considered here. *Cases 1* to *4* have been given rest periods of 2 to 4 months without showing evidence of regressive changes other than a decrease in number of erections. These observations are not interpreted as indicating that the effects are permanent, but suggest that continuous therapy is unnecessary. Our present plans, based on experience with this syndrome, as well as with other types of eunuchoidism, is to administer the androgen periodically alternating 3-month periods of hormonal administration and rest.

Urine was collected every week by 4 patients throughout the period of therapy. Gonadotropin assays were performed on each sample and occasional determinations of 17-ketosteroid and estrogen were made. Treatment with androgen was followed by a definite and fairly rapid fall in the excretion of gonadotropins. Although the excretion of gonadotropins was lowered in each case, the individual responses showed some variation. Thus in *cases 3, 4* and *6* the urinary gonadotropins remained higher than normal (fig. 19) while in *cases 1* and *2* they were no longer detectable in 12-hour specimens (fig. 20, 21). It should be noted here that the clinical course in these patients proceeded independently of the effect on urinary gonadotropins. The data suggest that excretion of luteinizing hormone is depressed early in the course of treatment and that excretion of follicle-stimulating hormone decreases with the continuation of therapy. The depression of gonadotropins is similar to

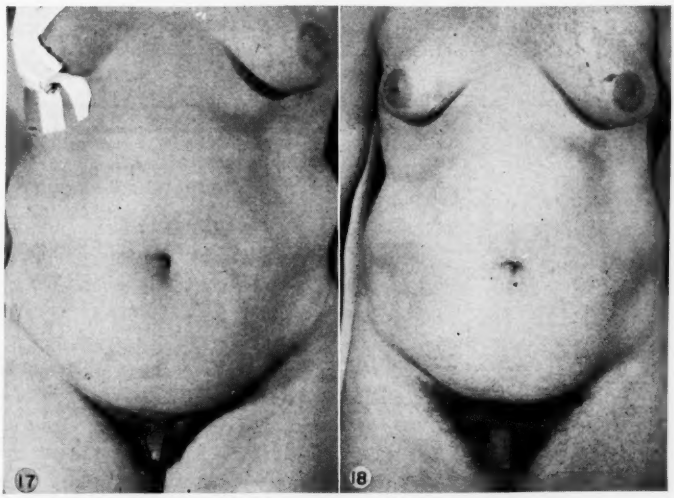
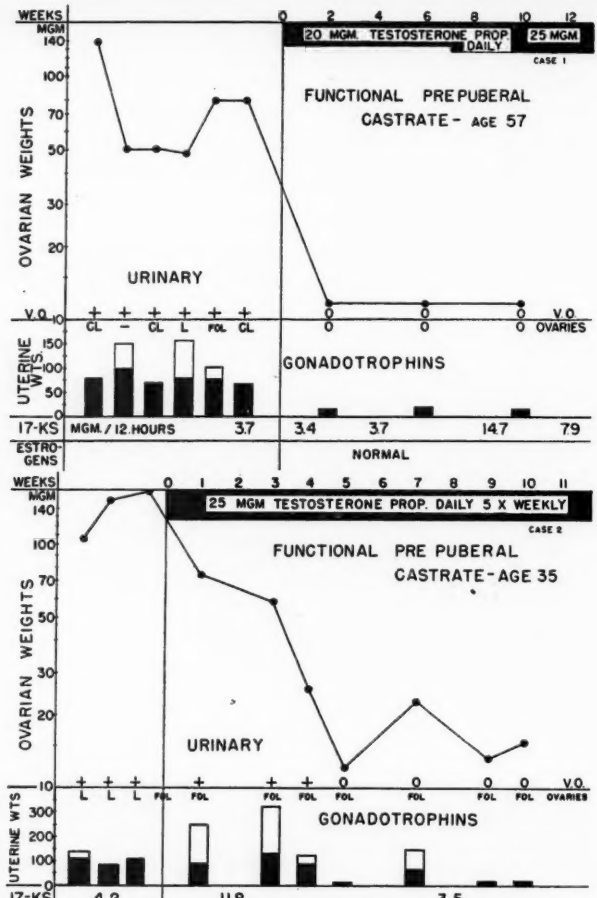


FIG. 17. *Case 4*, before therapy.
FIG. 18. *Case 4*, after only 50 injections of testosterone propionate in 25 mg. amounts given 5 times weekly for 10 weeks.



FIGS. 19, 20 and 21
(See next page for legend.)

that reported by one of us (C. G. H.) in the male climacteric and in castrated females. Changes in the level of gonadotropins is not the *modus operandi* for the clinical improvement since the latter occurs irrespective of the urinary titers of gonadotropin. However, our observations show that testosterone is capable of causing depression of pituitary gonadotropins when administered in large quantities.

Excretion of 17-ketosteroids was not altered significantly by the administration of testosterone propionate. The method of collecting the samples of urine must be remembered in interpreting this finding, which would appear to be contrary to the results of other investigators. Since collections were made 24 to 48 hours after the last injection of the week had been given, the peak excretion of the metabolites of testosterone probably was missed.

DISCUSSION

Absolute proof that each of the patients has complete testicular atrophy or anorchia is obviously not possible without necropsy examination. However, the circumstantial evidence is overwhelmingly in favor of this conclusion. *a*) Clinically the patients manifested sexual infantilism which is ordinarily associated with lack of gonadal function. *b*) Marked elevation of urinary gonadotropins. This phenomenon is known to follow gonadal failure. *c*) Biopsy of the scrotal contents in no instance revealed actively functioning testicular tissue, but did disclose Wolffian duct derivatives in each instance. In 3 cases more extensive exploratory operations, performed in the past, did not uncover inguinal or abdominal testes.

The diagnosis of bilateral anorchia is not without precedent and substantiation by autopsy findings. Up to 1938, when Rea (14) reviewed the literature, 11 cases had been studied at operation or at necropsy. Counseller and Walker (15) reviewed the literature in 1933. Some of the cases which have been reported were studied as infants or before puberty and in others complete clinical descriptions are lacking, but in general, the adults fit the clinical picture described in our cases.

Many examples of unilateral anorchia or atrophy are described in the literature, but the patients, of course, have no signs of eunuchoidism or infantilism. Andrews and Oslund (16) discuss autolysis of the testis and describe remnants of Wolffian duct structures found in one case.

The pathological process in our cases must antedate puberty because no patient has ever exhibited the usual signs of spontaneous sexual maturation. Since their testes are non-functional, we regard them as functional prepuberal castrates. It would appear that this clinical syndrome may arise from a variety of causes. In our cases at least 3 different etiological factors appear to have been responsible for the final clinical result. *Cases 1* and *2* may be grouped together as examples of atrophy due to a sclerosing process. Remnants of testes remaining in the scrotum and the absence of eunuchoidal proportions separate them clinically from the other four cases. The onset of gonadal failure in these two probably occurred later than in the others, and quite possibly the testes had some prepuberal and puberal function.

In *case 5* responsibility can be charged to surgical interference with the blood supply of the testes with resultant atrophy of seminiferous tubules and Leydig cells.

Failure of union between Wolffian duct derivatives and the testis with only the former descending into the scrotum is regarded as the most plausible explanation for the gonadal failure in *cases 3*, *4* and *6*. It is worth recalling that a series of complex embryologic events take place during the normal development and descent of the testes into the scrotum. During the sixth month of fetal life, the rete tubules, which develop within the primitive gonad, be-

FIGS. 19–21. Results of urinary gonadotropic assays performed on immature female rats, are indicated by several endpoints: *a*) ovarian weights in mg. are plotted against a logarithmic scale; *b*) ovarian appearance is indicated by CL for corpora lutea, L for diffuse follicular luteinization, FOL for follicles only, O indicates no stimulation; *c*) vaginal canals were open when a + is indicated opposite VO (for vaginal opening) and were closed in instances where an O appears; *d*) the solid black vertical bars indicate uterine weights after fluid had been expressed. The white bars indicate uterine weights before fluid was released. 17-Ketosteroids are indicated by 17-KS and expressed as mg. of androsterone per 12 hr.

Note in figure 21 that before treatment there was an association of large ovaries, corpora lutea and uteri which showed progestational changes as indicated by the finding of large uteri without fluid. After treatment the disappearance of LH from the urine is suggested by the lower ovarian weight, the presence of follicles only, and the increased uterine weight due to accumulation of intrauterine fluid. These observations indicate the presence of estrogen and the reduction or absence of progestin. In figure 19 and 20 both FSH and LH were completely suppressed as treatment progressed.

come continuous with the efferent ductules which form from the mesonephric tubules. The ductules connect with the epididymis which develops from the Wolffian (mesonephric) duct. Failure of union of these ducts results in a testis without a path of egress for spermatozoa. More important, from the standpoint of our present interest, is the failure of such testes to descend into the scrotum since the gubernaculum testis attaches to the Wolffian duct. Thus the derivatives of the latter, epididymis and vas deferens, will descend, leaving the testes in the abdomen. Clinical instances of this phenomenon are mentioned by Whiteford (17), Wood (18), Creavy (19) and Henry (20). However, if this situation occurred in *cases 3, 4* and *6*, the abdominal testes have not shown the degree of hormonal function usually associated with cryptorchid testes and it must be presumed that no functional testes were present. If the failure of tubular union in these patients was due to anorchia or to early atrophy of the testes, no degree of testicular function would be anticipated.

The finding of exceeding sparse pubic and axillary hair requires further comment. Fraser and his co-workers (21) have found almost complete absence of 17-ketosteroid excretion associated with an absence of pubic and axillary hair in panhypopituitarism. In our own cases of tall eunuchoidism associated with low titers of gonadotropin we have found abundant pubic and axillary hair associated with high normal excretion of 17-ketosteroids. The functional prepuberal castrate seems to lie between these two groups in that he shows intermediate development of pubic and axillary hair as well as intermediate excretion levels of 17-ketosteroids. This suggests a correlation between hair growth and the excretion of 17-ketosteroids. Albright, *et al.*, (2) have called attention to such a correlation in their group of short women with primary gonadal failure. The maintenance of the epididymis in 2 of our cases and of the prostate in *case 1* (biopsy revealed small ducts with normal epithelium and some small corpora amylacea) might also be ascribed to an androgenic effect of the 17-ketosteroids. These ketosteroids are obviously not derived from the testes and must be elaborated extra-gonadally, probably by the adrenal cortex.

The overall stature of the patients was short or normal. This was not associated with short extremities, as is commonly the case in short individuals, but with eunuchoidal or normal proportions. Eunuchoidal gigantism is usually associated with a delay in gonadal development, or pre-adolescent gonadal failure. Our experiences indicate that the delay in epiphyseal closure endures for about the same length of time in both tall and short eunuchoids, thus giving opportunity for growth in height to continue for longer than the normal time. The principal difference between the two types lies in the fact that the tall eunuchoid has testes which may be secreting androgen in minimal, or at least reduced amounts, while the short eunuchoid, as exemplified by our patients, has none. It is possible that this minimal secretion in the case of the tall eunuchoid may be sufficient to cause bone growth without inducing sexual maturation because of differences in the thresholds of response between growth and sexual maturation. This stimulus to growth is absent in the short eunuchoid.

The above explanation for the resultant stature in short eunuchoids seems contrary to the popular belief that eunuchs are invariably tall. However, in its support it is worth noting the findings of Wagenseil (25) who compared the stature of 250 normal Chinese men and the stature of 11 eunuchs who had been castrated between the ages of 9 and 16 years, during which time the epiphyses are presumably still open. When he examined the latter group at ages ranging from 47 to 74 years the stature of each subject was well within the range for normal Chinese men. Six eunuchs had attained statures above the mean, one at the mean, and four were shorter than the mean. The same author (26) studied 11 Sudanese and Abyssinian adults who had been castrated between the ages of 6 and 12 years. He found the stature of all to be within the range of normal for these races. Five were taller than average, two were average and four were shorter than average in height. These and similar observations on prepuberal castrates lend credence to the hypothesis that the gonadal androgens stimulate bone growth. It is, of course, well known that treatment with testosterone encourages bone growth and in addition induces closure of the epiphy-

ses. Therefore, variations in the eventual height of castrates and of functional prepuberal castrates must be dependent upon other factors and it is likely that tall functional prepuberal castrates will be encountered.

The failure of the iliac crests to complete their union with the ilium and the small to rudimentary size of the frontal sinuses indicate a retarded completion of osseous development yet epiphyseal closure had occurred in the long bones of all patients. Since such closure, although delayed, occurred in the absence of demonstrable testicular tissue of any sort in 4 cases, the relation of gonadal androgens to epiphyseal closure is subject to question. Perhaps gonadal androgens act to 'catalyze' or accelerate closure, a process that apparently will occur in the absence of such a 'catalyst,' or occurs because the 'catalyst' is derived from extragonadal sources as, for example, the precursors of the 17-ketosteroids.

The changes which have been observed in the breasts of patients with functional prepuberal castration are similar to those which we have observed in the breasts of patients whose testes show hyalinization of the seminiferous tubules associated with or in the absence of Leydig cell failure. This suggests that the gynecomastia in the two syndromes may have a common cause. In both instances urinary levels of estrogen tend to be subnormal, a fact which reduces the likelihood that estrogenic hormone is the factor responsible for the mammary changes.

Klinefelter, Reifenstein and Albright have advanced two explanations for the occurrence of gynecomastia in their syndrome of seminiferous tubule failure. The first explanation (22) supposed that the normal seminiferous tubules elaborated estrogen and that this ceased when the tubules became hyalinized. They further postulated that under normal conditions this estrogen prevents gonadal testosterone from stimulating mammary growth, but in the case of seminiferous tubule failure the gonadal testosterone is uninhibited and thus free to stimulate the male breast. Later (3) they substituted 'inhibin' for estrogen in the same explanation.

This explanation is inadequate for our cases since neither inhibin nor testosterone could have been secreted by their gonads and such an imbalance between the two could not have occurred.

We do not believe that we have sufficient evidence to formulate a sound explanation for the mammary changes which have been observed in the patients reported here or in our cases of the syndrome described by Kleinfelter, Reifenstein and Albright. However, an explanation which appears to be more reasonable than those advanced, would take into account the possible mammogenic activity of the 17-ketosteroids produced by these patients. A paucity of information exists concerning the physiological activities of substances grouped together under the heading of 17-ketosteroids and it is not unreasonable to suppose that some of them or their precursors may stimulate mammary changes.

Testosterone therapy in our cases has had no marked effect upon the size of the breasts, although a longer trial is necessary before this fact is assured. *Case 3*, whose mammary tissue showed the least departure from normal, had intermittent androgen therapy for 6 years prior to the biopsy. This suggests that testosterone propionate tends to discourage rather than stimulate mammary growth.

SUMMARY

Six examples of a new syndrome occurring in males is described, including accounts of the symptomatology, diagnosis and treatment.

Clinical signs included lack of sexual maturation associated with undeveloped genitalia, absence of ejaculations, sparse female escutcheon and sparse axillary hair, absence of hair on body, extremities and face, high pitched voice, gynecomastia (in some), eunuchoidal proportions, lack of muscular development, small prostate gland. Symptoms included nervousness, easy fatigability, lack of strength and endurance and an anti-social psychoneurotic tendency.

The diagnosis was made by finding, at biopsy, that the testes were completly atrophic or absent, but that Wolffian duct derivatives were present in the scrotum. Biopsy of the mammary glands revealed deviations from normal male breast structure. Two constituents of the gonadotropic hormone complex, *viz.*, follicle-stimulating hormone and luteiniz-

ing hormone, were markedly elevated in the urine. 17-Ketosteroid excretion was low normal or depressed. Estrogen excretion was less than normal. Osseous development and time of epiphyseal closure were delayed.

Substitutional therapy with testosterone propionate administered in 25-mg. amounts 5 times weekly caused sexual maturation analogous to that occurring spontaneously at puberty. Estrogen excretion increased to normal levels. Urinary gonadotropins were depressed, luteinizing hormone apparently disappearing from the urine before follicle-stimulating hormone was markedly lowered.

An attempt has been made to account for the absence of testes, the occurrence of mammary development, the combination of short stature and eunuchoidal proportions, and the source and physiological activities of the 17-ketosteriods produced by these patients.

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Observations on the Effect of Chorionic Gonadotropic Hormone and Male Sex Hormone on Eunuchoidism

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It is believed that our observations concerning the effects of endocrine treatment upon genital development, cryptorchidism, linear growth, bone development and behavior and personality changes in three male eunuchoids of the preadolescent type warrant description. One is a prepubescent boy of 10 years and 11 months and the other two are adults of 30 and 32 years, respectively.

The bone development was measured by a modification of Todd's standards (1), and the height and height increase by the Baldwin-Wood standards for the medium average (2). Routine hematological and chemical studies of the blood and urine were made by accepted standards. The basal metabolic rate was determined on the basis of actual weight by the Boothby and Sandiford modification of the Du Bois standards. The specific dynamic action of protein was determined by the modification of Goldzieher and Gordon (3).

CASE REPORTS

Case 1. L. E. This boy was referred at the age of 10 years and 11 months because "he was growing too rapidly, was slow in school and was temperamental in his behavior." He had received roentgen therapy at the age of 2 years for "an enlarged thymus." His developmental history revealed a delay in walking and talking; the family history was irrelevant.

He had grown 9 in. in height in the preceding 3 years. At the time of our first examination, the height was 67 in. with an upper longitudinal measurement of 31 in., a lower longitudinal measurement of 36 in. and a span of 69 in. The body configuration was typically eunuchoidal with a slim torso, disproportionately long and thin extremities with poorly developed musculature and soft, smooth skin. The external genitalia were markedly underdeveloped; the scrotum was small and contained both testes which were soft and tiny.

Hematological and urinary findings were normal. During fasting, the blood chemistry values per 100 cc. were: uric acid, 4.1 mg., glucose, 86 mg., chlorides, 492 mg., and cholesterol, 195 mg. The basal metabolic rate was minus 24 per cent and the specific dynamic action of proteins, 5 per cent. A skull roentgenogram was essentially normal. The bone age as estimated from roentgenograms of the wrists was equivalent to that of a normal male of 12 years and 3 months.

The patient was treated with chorionic gonadotropic hormone,[1] receiving 500 rat units twice a week for 8 months (total, 12,200 R.U.). During this phase of treatment, the penis became somewhat larger, the testes increased in size and became firmer and the scrotum became more turgescent and longer.

Treatment with testosterone propionate[1] was instituted at the age of 11 years and 6 months; the height at this time was 69¼ in. and the bone age, 13 years and 3 months. The dosage for the first 2 months was 10 mg. twice a week and 25 mg. twice a week for the following 2 months. The maintenance dose thereafter was 10 mg. twice a week but of the total period of treatment (20 months), he actually received the male sex hormone for only 14 months, the total dosage being 1,470 mg. Within 2 weeks after starting this treatment, the penis became turgid and appeared thicker and longer; the scrotum became more redundant and corrugated, but the testes did not show much gross change. A few strands of hair soon appeared about the base of the penis. During the next two months occasional erections were experienced. Subsequently his voice "began to crack," and became huskier; a slight acneiform eruption appeared over the forehead and nose. The size and thickness of the phallus and the amount of pubic hair progressively increased. With a reduction of the dosage to 10 mg. of testosterone propionate twice a week, the size of the external genitalia and the frequency of erections decreased. At the end of the treatment period, at the age of 13 yr., 4 mo., the

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[1] We are indebted to Dr. Leo A. Pirk of Roche-Organon, Inc. Nutley, N. J., for generous supplies of chorionic gonadotropic hormone (Pregnyl), testosterone propionate (Neo-Hombreol), and methyl testosterone (Neo-Hombreol, M), the materials used for treatment of all patients discussed.

external genitalia were larger than in the case of a normal 15-year-old boy. There was a heavy growth of pubic hair, a moderate amount of axillary hair and a beginning growth of facial hair. His voice was lower in pitch. Psychologically, he had become more alert and aggressive and manifested a definite interest in girls. He experienced frequent nocturnal emissions and resorted to occasional masturbation. He was 74¼ inches tall and the extremities were disproportionately long. The osseous development was advanced to that of a normal 15-year-old boy.

The patient remained under our observation for 2 years and 4 months without receiving further therapy. At the end of this period the chronological age was 15.5 years while the bone age was equivalent to that of a 17-year-old male. He had grown to a height of 78.5 in.

Case 2, M. L. This patient was referred at the age of 30 years, because of emotional instability, genital underdevelopment and undescended left testis. He felt "socially handicapped" because of his youthful and effeminate appearance. He was shy and retiring, had a high-pitched voice and felt embarrassed because he "shaved only once per month." Although he enjoyed social activity, he restricted himself on account of his physical handicaps and also because of his lack of interest in the opposite sex.

In general appearance he seemed at least 10 years younger than his actual age. He was 69 in. tall and weighed 200 pounds. The extremities were disproportionately long and slender. The skin was dry and smooth and there was no facial hair. A few strands of axillary hair were present and the scant pubic hair had the feminine distribution. The voice was piping and effeminate. Fat deposition was pronounced in the mammary and subscapular areas, the abdomen and the buttocks. There was a moderate gynecomastia and predominant girdle obesity. The penis measured 1.5 in. in length and was hidden in pubic fat. The scrotum was short, slightly wrinkled, and had no hair; the right testis was small and soft and was located in the mid-scrotum, while the left testis was not palpable. Routine laboratory procedures revealed essentially normal findings. The bone age was 17 years. The fusion of the epiphyses of the radius and ulna was incomplete.

Treatment with testosterone propionate was instituted in January, 1940, with a dosage of 25 mg., three times a week. A month later the phallus had increased in size and was turgid; the scrotal skin had become thick, redundant and corrugated; there was an increase in hair growth over the entire body. The voice had become deeper, and aggressivness had increased.

At the end of 24 weeks, during which he received 1800 mg. of testosterone propionate, the right testicle remained in about the same position but the left could be palpated and forced temporarily into the lower third of the inguinal canal. The patient experienced occasional erections without emissions. He shaved more frequently (about once a week) and noted a development of facial acne.

For 5 months, beginning in July, 1940, 500 R.U. of chorionic gonadotropic hormone was administered twice or three times a week, the total being 19,000 units at the end of the third month and 27,000 at the end of the fifth. During this period there was a slight regression in the turgescence of the penis. The descent of the cryptorchid testis was more rapid than during the period of treatment with testosterone propionate. The left testis became larger, firmer, tender and descended temporarily to the upper pole of the scrotum. There was no apparent change in general physical condition or psychological behavior except that he did not feel as aggressive and did not experience as many erections as previously. Gonadotropic treatment was discontinued on Dec. 1, 1940.

Methyl testosterone[1] by mouth was then given in an average daily dosage of 50 mg. for 3 months (total 4200 mg.). In January, 1941, the patient's voice became huskier and lower in pitch and the phallus increased in size and became turgid; the change was not as rapid, however, as previously observed under treatment with testosterone propionate. Erections and nocturnal emissions occurred. A decidedly more aggressive attitude was noted, he was more vigorous and more active socially and more attracted to the opposite sex but did not indulge in sexual relations. He now had a fairly heavy growth of facial hair and a marked growth of pubic and body hair. As treatment progressed, the patient's libido gradually increased in spite of reduction of the dose to 30 mg. of methyl testosterone daily for the next 8 months. At the end of this time, his voice had assumed a more normal masculine timbre and he had a greater desire for feminine companionship. The penis became normal in size, the scrotal changes were maintained, and the prostate became palpable. The left testis, however, diminished in size and retracted to the lower third of the inguinal canal. With resumption of chorionic gonadotropic hormone for one month, during which time he received 500 units twice a week, the left testis again appeared in the upper pole of the scrotum and increased in size. Two months after termination of this treatment, he was contemplating marriage. The height at this time was 69.5 in. and his bone age 18 years.

Case 3, B. G. This patient came under observation at the age of 32 years because of lack of "normal development." He felt "inferior" because he appeared youthful, had a high-pitched voice and was "clean-shaven." He had no social interests nor any desire to participate in any activity outside of his work.

He presented an appearance of a stout 16-year-old boy, with an obesity of the shoulder, mammary, trunk and girdle regions. The measurements were: height, 62.5 in. with an upper longitudinal measurement of 28 in. and a lower longitudinal measurement of 34.5 in.; span, 67.5 in.; weight, 144.5 pounds. The facial hair was lacking, the skin smooth and the extremities slender, tapering and disproportionately

long. The pubic hair was sparse; the phallus measured 1.5 inches in length and was buried in pubic fat; the scrotum was short and puerile. The left testis which was in the upper pole of the scrotum was the size of a small lima bean. The right testis was soft and smaller than the left and could be palpated in the lower third of the inguinal canal. Roentgenograms of the carpals showed a bone age of 17 years. The epiphyses of the radius and ulna were not completely united.

Treatment with testosterone propionate was begun in doses of 25 mg. twice a week. Within 2 weeks the penis was thicker and slightly longer. In 4 weeks, the scrotum was slightly elongated and more 'pouch-like' in shape. The right testis was slightly larger and could be forced into the external inguinal ring. The left testis was larger and firmer. There was a slight increase in the amount of pubic hair and slight facial hair growth. Erections occurred about every 2 to 3 days.

At the end of 2 months the phallus measured 3 in. in length and 1 in. in circumference. The right testis could be forced manually into the scrotum which had become furrowed and longer. Psychologically, the patient had not changed much and did not exhibit any aggressive tendencies. His voice remained unchanged. After further treatment with testosterone propionate in the same dosage for an additional month, the patient became more aggressive and exhibited a slight interest in the opposite sex. He also experienced more numerous erections, his voice became huskier, and he now shaved every 2 weeks.

Testosterone propionate was discontinued after a period of 3 months and chorionic gonadotropic hormone was administered twice a week in doses of 500 I.U. During the next 6 months, a total of 24,000 I.U. was given. Both testes became larger and firmer during this phase of treatment and the right testis was in the upper pole of the scrotum, but retracted occasionally. There was a slight increase in the size of the phallus. There was no increase in stature.

Subsequently, methyl testosterone in daily doses of 20 mg. was given by mouth for 2 months, together with chorionic gonadotropin administered parenterally, twice a week, in doses of 500 I.U. During this phase, the patient's voice became somewhat huskier, the phallus more turgid, and he experienced more frequent nocturnal emissions. He worked more energetically and did not tire easily. As treatment continued, he experienced an increase in libido and exhibited a definite interest in the opposite sex, but did not indulge in coitus. At the termination of treatment, which had been continuous for 11 months, his height was 62.5 in. and the bone age was 17.5 years.

DISCUSSION

Endocrine therapy has been used satisfactorily in the treatment of many hypogonadal conditions. In preadolescent hypogonadism which results from either primary testicular deficiency or inadequate pituitary gonadotropic stimulation, the best initial therapy, we believe, is chorionic gonadotropic hormone (4). The most effective forms of such stimulative treatment are preparations obtained from pregnancy urine. If there is no response or a very poor reaction to this initial form of therapy, androgenic hormone should be substituted. Pullen (5, 6), believes, however, that those patients who respond to gonadotropic therapy should not be kept on this form of treatment indefinitely, but that treatment should be interrupted, evaluated, and continued with either chorionic gonadotropic hormore or testosterone propionate depending upon the response of the patient.

Numerous clinical reports have shown conclusively that intramuscular injection of testosterone propionate has been very effective in producing genital growth and the development of secondary sex characteristics (7, 8). Percutaneous inunction of a male hormone preparation (8) and implantation of crystalline testosterone pellets (9) were not as efficacious as the intramuscular route but were adequate in creating a maintenance response. The oral administration of methyl testosterone is equally effective as injections of testosterone propionate if about 5 times the parenteral dose is given (10, 11, 12).

Results of combined androgenic and gonadotropic treatment upon hypogenitalism and cryptorchidism. The striking physical effects of the administration of chorionic gonadotropic hormone and testosterone propionate in producing pubertal changes in both the pubescent and adult types of preadolescent eunuchoidism are well exhibited in the three case reports. We have observed that testosterone propionate (as substitutive androgenic therapy) is more effective in producing a greater degree of pubertal development than chorionic gonadotropic hormone (as stimulative therapy). Also the effect of the former is maintained for a longer time. Successive treatment with both agents is more effective in improving genital hypoplasia and the development of secondary sex characteristics than chorionic gonadotropic hormone alone. The combined treatment prompts normal pubertal changes as evidenced by a loss of feminine appearance with the appearance of the male type of body build, an increase in

pubic, facial and body hair, deepening of the voice, enlargement of the external genitalia, occasional erections and nocturnal emissions. The older patients experience a stimulation of libido with an awakening interest in the opposite sex, in addition to the normal pubertal responses. But of far greater importance are the social adjustments which enable them to assume a more normal rôle in society.

The effect on cryptorchidism in an adult was manifested in the patient *M. L.* (30 years of age) who presented originally an undescended left testis which was not palpable. Three months of treatment with 1250 mg. of testosterone propionate produced a partial response which was evidenced by the descent of the testis from its position in the abdomen into the lower third of the inguinal canal. With manipulation, the testis could be forced temporarily into the upper pole of the scrotum. Ultimate and complete descent of the testis into the scrotum was produced by the subsequent administration of 27,000 I.U. of chorionic gonadotropic hormone over a period of 5 months.

In the third patient (*B.G.*, 32 years old) who exhibited the obese form of eunuchoidism with unilateral cryptorchidism, initial treatment with testosterone propionate produced a partial descent of the testis after 2 months. Subsequent treatment with chorionic gonadotropic hormone produced a more rapid descent of the undescended orchis as evidenced by the fact that after receiving 24,000 I.U. in 6 months the testis was situated in the upper pole of the scrotum. Maintenance therapy with methyl testosterone and chorionic gonadotropic hormone for 2 more months assured permanent descent of the testes and an enlargement of the genital apparatus.

Results of combined androgenic and gonadotropic treatment upon height and bone development. The therapeutic effects of the synthetic androgens and the gonadotropic hormones in hypogonadism and cryptorchidism have been fully recognized but the influence of these substances upon linear growth and osseous development has been reported only recently (7, 12–16).

Normally epiphyseal union parallels sexual maturity and normal linear growth. But eunuchoidism orginating in childhood (prepubertal eunuchoidism) may be accompanied by a marked delay in epiphyseal maturity which subsequently leads to a late closure of the epiphyses. The ultimate height depends upon the activity of the anterior pituitary growth hormone.

Jaffe and Brockway (17) in their studies of 14 young males with cryptorchidism and hypogonadism and eunuchoidism observed that 4 of the cryptorchid patients had an abnormal rate of growth as a result of treatment with male sex hormone. A 16-year-old eunuchoid male grew 8 in. in 2 years after receiving testosterone propionate. They noted that there was no premature closure of the epiphyses and that the rate of growth was definitely increased above the normal.

McCullagh and McGurl (18) studied the effects of replacement therapy with testosterone propionate in adult eunuchoid males and found that the epiphyseal lines remained open "beyond the age period of their physiologic closure" but prolonged therapy lead to accelerated epiphyseal union.

Webster and Hoskins (16) found in their series of 8 hypogonadal boys, who were given testosterone propionate in doses of 75 to 125 mg. weekly over a period of 100 weeks, that the boys grew more than "twice as fast as before treatment was given or after it was discontinued."

Some variable results were obtained by Goldzieher (13) in his studies of the effect of the sex hormones on growth. He observed that excessive growth was curbed in some instances. On the other hand the rate of linear growth of 9 boys and 2 girls with retarded growth was accelerated.

Pullen (6) induced growth responses in 5 patients ranging in age from 15.5 to 19 years with 10-mg. doses of testosterone propionate. No acceleration in skeletal development resulted. However, he observed that in 2 patients who received 25 mg. of testosterone propionate 3 times a week for prolonged periods the bone age became abnormally accelerated.

In a previous communication we concluded (14) that chorionic gonadotropic hormone and testosterone propionate have stimulating effects on height and bone development in prepubertal and adolescent boys. There was

no premature closure of the epiphyses nor stunting of growth. Both hormones are of value in the treatment of preadolescent short stature.

The results in our three patients with hypogonadism showed that there was no correlation between the effect on genital development and that on linear growth and bone development. One adult (*B.G.*) did not increase in height but did show a slight advancement in bone age, equivalent to an increment of one-half year, after one year of treatment. The second adult grew one-half inch in height and advanced 1.5 years in bone development during 18 months of treatment. The younger adult eunuchoid (*M.L.*) showed a greater response in both height and bone development. At the end of 1.5 years of treatment, the height was 69.5 inches (a total growth of 0.5 in.) and the bone age was equivalent to that of a normal 18-year-old boy.

These two patients are examples of adult males with hypogonadism who had not undergone the normal pubertal changes. As a result of inadequate gonadal function they remained at a dormant prepubertal level but after adequate treatment they responded in the same manner as normal pubescent boys.

Treatment did not materially effect the height of the boy (*L.E.*) with eunuchoid gigantism. He had grown 9 in. in height in the 3 years prior to treatment and grew an additional $7\frac{1}{4}$ in. during 28 months of treatment. The latter increase is at the rate of 9.3 in. in 3 years, the same rate as that before treatment.

TABLE 1. EFFECT OF TREATMENT WITH CHORIONIC GONADOTROPIC HORMONE AND TESTOSTERONE PROPIONATE ON HEIGHT AND BONE DEVELOPMENT IN PREADOLESCENT EUNUCHOIDISM (*L. E.*)

Chronological Age		Height	Actual Ht. Increase	% Increment Above and Below Normal	Duration of Treatment	Bone Age		% Increment Above Normal	Treatment
yr.	*mo.*	*in.*	*in.*			*yr.*	*mo.*		
					Before Treatment				
7	11	58							
8	5	$59\frac{3}{4}$							
9	10	63							
10	4	64							
10	11	67							
			9	+50	3 yr.	12	3	+13	No treatment
					During Treatment				
10	11	67				12	3		C.G.H.[1] started, given 8 mo.
11	6	$69\frac{1}{4}$	$2\frac{1}{4}$			13	3		T.P.[2] started
12	8	$72\frac{1}{4}$	3			14	0		
13	4	$74\frac{1}{4}$	2			15	0		Treatment discontinued
			$7\frac{1}{4}$	+38	28 mo.	15	0	+18	
					After Treatment				
14	10	78	$3\frac{3}{4}$	−34	18 mo.	16	6	+36	
15	6	$78\frac{1}{2}$	$\frac{1}{2}$	−28	8 mo.	17	0	Normal	
			$4\frac{1}{4}$	−31	26 mo.				

[1] CGH, chorionic gonadotropic hormone
[2] T.P., testosterone propionate

After therapy was stopped, he grew only $4\frac{1}{4}$ in. in the next 28 months.

However, a growth of 9 inches in 3 years between the ages of 8 to 11 years is not equivalent to a like increase between the ages of 11 to 14 years. If it is valid to apply the average rate of height increase in normal boys between the ages of 8 to 15 years to the excessive increase in this boy, then we may evaluate the effects of treatment upon the percentage above or below the normal increment and not upon the actual number of inches grown at a given time. Upon this basis, the height in the 3 years immediately preceding the onset of treatment was at the rate of 50 per cent increase above the normal increment for that age and duration; that during treatment was equivalent to an

increase of 38 per cent above the normal increment and that after therapy was stopped, was at the rate of 31 per cent below the normal increment. This implies that during treatment there was a slowing down of an already accelerated linear growth; the height increased at a slower rate than before treatment but it was still above the normal increment. There was a marked drop in the rapidity of growth after treatment was stopped. This may further imply that any stimulation which may have been present during this time ceased after treatment was discontinued. On the other hand, it may be inferred that this subsequent drop in the rate of height increase was consistent with a markedly advanced bone growth (17-year equivalent at the end of the period of observation).

The accelerated rate of bone development noted at the time therapy was initiated continued during the period of treatment, but this did not continue to complete closure of the epiphyses of the long bones. Before treatment was started, the boy's bone age was 1 year and 5 months above the normal, equivalent to an increase of 13 per cent above the normal. The bone development advanced 33 months in 28 months of treatment, at the rate of 18 per cent above the normal increment. Discontinuance of treatment was followed by a spurt in bone development for the next 18 months at a rate of 38 per cent above the normal increment. Subsequently, this tapered down to the normal rate of osseous development. At the age of 15 years and 6 months the bone age was equivalent to that of a 17-year-old male. We cannot explain the marked increase in the rate of osseous growth after therapy had been stopped.

SUMMARY

The effects of testosterone propionate, chorionic gonadotropic hormone, and methyl testosterone upon genital development, cryptorchidism, growth in stature, bone development and personality changes are reported in 3 males with preadolescent types of eunuchoidism. One was a boy of 10 years and 11 months and the other two were adults, 30 and 32 years old, respectively, with obesity and unilateral cryptorchidism. Normal pubertal responses were produced in all 3 patients by treatment with these hormones.

Testosterone propionate and methyl testosterone alone or in alternation with chorionic gonadotropic hormone were effective in the treatment of hypogenitalism. Methyl testosterone maintained the effects of androgenic therapy and was found to be an adequate, substitutive form of male sex hormone. Testosterone propionate produced a partial descent of the testes in both adult eunuchoid males. Supplementary treatment with chrionic gonadotropic hormone produced their complete descent.

Chorionic gonadotropic hormone and testosterone propionate did not have any clear effect on either height increase or bone development in the boy with eunuchoid gigantism. There was a slowing down of an already accelerated linear growth but he continued to increase in height at a greater increment than normal. The slightly advanced bone development continued at practically the same level of increase without the induction of epiphyseal closure.

Both adult eunuchoids showed slight progress in osseous development, but the epiphyses remained open during the period of observation. The height was slightly increased in one patient and remained stationary in the other.

All three patients showed a measurable improvement in their psychic development. Their behavior became more agressive and they exhibited more interest in the opposite sex and in their social undertakings and occupational pursuits.

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A Clinical, Laboratory and Pathological Study of a Partially Hypophysectomized Human Female

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IN A previous communication in 1936 (1) the effect of estradiol and anterior pituitary gonad-stimulating hormone was reported in a supposedly completely hypophysectomized colored female and other laboratory data were presented. Since that time, the patient has had repeated laboratory and clinical studies until her death Jan. 31, 1942. These data (table 1), together with significant pathological findings, are presented. The patient was admitted in January, 1942, *in extremis*, having been acutely ill only 48 hours. She died before a clinical diagnosis could be made. A provisional clinical diagnosis of hypoglycemia, pituitary deficiency, and pyrexia of unknown origin was made. Pathologically there was an acute bronchitis with pulmonary edema and hydrothorax, together with ascites. No evidence of acute abdominal inflammation other than ascites was noted. It should be noted that an estimated 10 per cent of the anterior lobe of the pituitary gland remained.

The B.M.R., which dropped to low levels soon after operation, remained low in spite of apparent adequate doses of desiccated thyroid. The low blood pressure and slow pulse are in keeping with the low basal metabolic rate. Change in body weight was not remarkable in spite of the low metabolism.

The blood chlorides were not remarkable. The urine chlorides varied from 210 to 690 mg. per cent with determinations soon after operation and 4.5 years later were about the same. This is of interest in view of the pathology noted in the adrenal glands. The values for blood calcium, phosphorus, total protein, NPN, uric acid, creatinin and CO_2 were not remarkable. Nothing conclusive can be said about the blood cholesterol in spite of the low B.M.R. The blood sugar dropped to low levels, and several sugar tolerance curves were flat.

None of these laboratory findings were markedly influenced by the injection of hormone preparations. In November and December, 1938, 240 to 540 rat units of mare's serum gonadotropic hormone[1] was given. No endometrium was obtained on biopsy and no changes were noted in laboratory findings. In January, 1941, 4000 rat units of a sheep gonadotropic hormone[2] was given over a period of 10 days. No endometrium could be obtained on biopsy and there was no subsequent change in laboratory data.

AUTOPSY REPORTS

This patient was autopsied in January, 1941. The significant findings included absence of axillary and pubic hair. Both were present before operation, and were gradually lost over a period of the next two years. The external genitalia were atrophic. The breasts consisted of collagenous fibrous tissue which showed moderate

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[1] Pregnant mare's serum (Gonadogen), the Upjohn Co., Kalamazoo, Mich.

[2] Anterior pituitary gonadotropin (Preloban), Winthrop Chemical Co., New York City.

TABLE 1. LABORATORY AND CLINICAL DATA IN THE CASE OF A PARTIALLY HYPOPHYSECTOMIZED HUMAN FEMALE WITH 10% OF THE GLAND REMAINING

Date	Chloride		Blood Chemistry									B.M.R.	Blood Pressure	Pulse	Wt.
	Blood	Urine	Ca	P	Total Prot.	NPN	Uric Acid	Creat.	CO_2	Chol.	Sugar				
	mg.%	*mg.%*	*mg.%*	*mg.%*	*mg.%*	*mg.%*	*mg.%*	*mg.%*	*vol.%*	*mg.%*	*mg.%*	*%*	*mm. Hg.*	*per min.*	*kg.*
1935															
10–2	492	690	9.9	5.5					52		92	− 3		70	54.8
10–21	422										70		108/60		
10–28	468										53				
11–6		327									70	−29		56	51.5
11–17	468	223													
1936															
1–17		456				24	3.0		58	213	75	−33			
1–25			10.1	4.6			2.0					−33			
2–19												−23			
3–2												−27			
3–11		210													
4–7												−22			
10–31	538		10.1			23	3.6	1.5	58	300	50	−16	80/60	56	53.6
11–10												−33			53.0
1938															
4–19	596				6.9	23	3.2	1.7		306	51	−25		94	63.6
5–23						23	3.6	1.5	62	300	45	−35		56	63.6
7–2												−25		68	51.8
8–12						26	2.0			187		−37		60	52.6
11–3	574			3.4	6.8	33	3.6	1.5	62	350	50	−37		56	58.6
12–16	580									237		−47		72	60.2
12–22			9.8	4.6	6.9	32	4.4	1.6	76		74	−47	78/60	54	60.2
1939															
2–5		585	10.6	3.8			2.8		62	175	50	−46	80/60	58	63.0
4–7														58	63.0
9–13		576	9.2	3.8		27	2.8	1.2	58	150	70	−21		60	55.6
1940															
1–31		574	14.0	4.0	6.9		4.0	.9	54	275	62	−33	80/60	60	58.0
9–23		593	10.7	4.4	6.6	30			43		63				
1941															
10–10		566				19						−36			
1942															
1–27		625			6.7	31			39		59		72/45		
1–31	Death, Autopsy.														

edema. A small amount of fat was present. Only a few acini and ducts were present.

mhe liver which weighed 1410 gm., the heart, 260 gm., and the kidneys weighing 150 and 130 gm. each, were grossly and microscopically normal. Nothing unusual was noted in any of the somatic or visceral blood vessels and the skeletal muscle was not remarkable.

Pancreas. The pancreas weighed 50 gm., was normal in size and shape, and pink in color. It contained a moderate amount of fat, and the lobulations were regular. On cut section the lobules separated easily. The duct was patent, and the islets were visible as tiny pale yellow dots. Interlobular connective tissue was increased in amount and edematous. The acini were regular, islet tissue was abundant and the cells appeared normal.

Adrenal. The adrenal glands were extremely thin, the flat surface measuring 2×2 cm. They were pale yellowish-gray in color, and on the surface a number of small islands of yellow issue were seen beneath the thin translucent capsule. The cut section measured less than 1 mm. in thickness. All that remained were two thin pale grayish strands of tissue which were closely approximated with no grossly visible medulla between. Microscopically, the adrenal glands were markedly atrophied. The cells in the outer portion of the cortex had a pink granular cytoplasm; most of the remaining cells showed vacuolization and disintegration. The surrounding

capillaries were congested. There was some fibrosis, with connective tissue extending between the strands of cortical cells. A very small amount of medullary tissue remained.

Pelvic organs. The vaginal mucosa was somewhat toughened and gray in appearance. The cervix was small, round, smooth and patent. The uterus and adnexae showed marked atrophy. The uterus was 4 cm. in length. The myometrium was pale gray in color, firm and measured 1 cm. in thickness. The endometrium was smooth and gray. The fallopian tubes were patent. The ovaries were oval in shape and measured 1 cm. in diameter. The capsule was thickened and pale in color, and contained a number of small cysts which measured 3 mm. in diameter and were filled with a clear yellow fluid. The germinal epithelium of the ovaries contained many small primary follicles and a few growing follicles. There were several large cystic spaces which were filled with a granular pink exudate and lined with stratified epithelium. Several atretic follicles and one old corpus albicans were seen. The medulla consisted of loose connective tissue and numerous thick-walled arteries. The endometrium of the uterus was markedly atrophied, and all that remained was a single layer of low cuboidal epithelium and a few glands. The cervical epithelium was absent.

Thyroid, parathyroid and thymus. The thyroid gland was markedly atrophied, and the upper pole was absent on the right side. The weight of the entire gland was 1 gm. It was soft, and pale reddish-pink in color. The cut surface was uniform and no nodules were present. On the surface of the upper portion of the right lobe lay a parathyroid gland. This was oval in shape, soft, red in color, and measured about 3 mm. in diameter. Lying in a small pad of fat beneath the manubrium were several small round, moderately soft areas of gray thymic tissue. The follicles of the thyroid were small. They were lined by a low cuboidal epithelium and contained a clear pink colloid. The interstitial connective tissue was moderately increased in amount and was spread diffusely throughout the gland. Several small patches of thymic tissue were present, separated by large amounts of fat and edematous connective tissue. Most of the thymic tissue appeared to be medullary in type. The reticular network was easily distinguished and Hassal bodies were seen.

Hypophysis. The pituitary gland consisted of a small flabby piece of pink tissue without definite form. Serial sections showed a small amount of anterior lobe which measured 2 mm. in width and 4 mm. in length, which was about 10 per cent of a normal lobe. It was composed of groups and columns of cells which were supported by a delicate reticular connective tissue. Between these were dilated empty sinusoids. About one half of the cells were chromophile and the other half chromophobe. Most of the chromophile cells had an eosinophilic cytoplasm. A few small cystic areas lined by a low cuboidal epithelium and containing a small amount of granular pink material represented the remainder of the pars intermedia. The stalk and the remnants of the posterior lobe measured approximately 2 mm. in width and 6 mm. in length. They were composed of fusiform and irregularly shaped cells with delicate processes extending from them. Only a few small blood vessels were present. Dense collagenous fibrous tissue surrounded the anterior lobe and a portion of the posterior lobe and stalk.

Pineal. The pineal body was normal in size and position. The posterior half of this gland was replaced by a small cyst. It showed strands of cells with indefinite outlines embedded in a reticular network. Most of these cells had a pale pink cytoplasm with large round darkly stained nuclei. Several small areas of calcification were present.

DISCUSSION

For obvious reasons, conclusions from one case are withheld. It is interesting to note that in a young human female life was maintained with as little as 10 per cent of the anterior lobe of the pituitary gland. The most marked laboratory and clinical effects of the deficiency were hypotension, low B.M.R., and low blood-sugar level. The low blood-sugar level is in keeping with a normal pancreas in the absence of the anterior lobe of the pituitary gland. Hart and Magiday (2) have shown that total removal of the hypophysis produces a drop in fasting blood sugar to hypoglycemic levels without the production of shock. They maintain that the level of blood sugar is not wholly dependent on the pituitary gland, and that the pituitary gland functions as a mechanism for raising the blood-sugar level and they conclude that the pituitary gland is not essential. Stephens (3) reporting on the chloride excretion test in pituitary failure, recorded normal values in this case. The test was made three years after operation. One should question the value of this test in pituitary and adrenal failure. Obviously more than 10 per cent of the anterior

lobe of the pituitary gland must be necessary in the human being to maintain gonadal function. Other normal laboratory findings are difficult to explain in view of the marked atrophy of the ductless glands, animal experimental work to the contrary.

SUMMARY

A clinical, laboratory, and pathological study of a partially hypophysectomized human female is presented, showing that life can be maintained with as little as 10 per cent of the anterior lobe of the pituitary gland. Significant findings were low B.M.R., hypotension, low blood-sugar level, marked atrophy of thyroid, adrenals, ovaries and breasts; absence of axillary and pubic hair, and atrophy of the reproductive system.

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Plasma Vitamin C Levels in Women During the Menstrual Cycle

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PHILLIPS, *et al.* (1, 2) demonstrated a marked increase in the plasma vitamin C level of cows on the day they came into heat. This increase was maintained for only a short time and the vitamin C in the plasma was back to the basal level 14 hours later. This has been confirmed by Sutton, *et al.* (3). The Wisconsin workers found a close correlation between the occurrence of these peaks of plasma vitamin C in cattle and the ability to breed them. In some cases, sterile cows, which showed no structural abnormalities of the reproductive tract, were converted into fertile ones by injecting intravenously large amounts of vitamin C just before breeding them.

An attempt has been made in this study to determine whether women show a similar rise in the vitamin C content of fasting plasma during the menstrual cycle.

EXPERIMENTAL PROCEDURE

Most of the 8 subjects were nurses who received their meals at the Hospital dining rooms. Samples of fasting blood were obtained throughout the menstrual cycle. When the periods were regular, samples were taken on the 14th, 15th and 16th days before the onset of the next menstruation. In all cases, the needles and syringes were flushed out with sterile isotonic sodium citrate solution in order to avoid as far as possible any hemolysis in the blood. The blood was transferred to a centrifuge tube containing 3 drops of 20 per cent potassium oxalate which was gently inverted to distribute the oxalate. Within an hour after the sample was drawn, the vitamin C analysis on the plasma was started. A modified Mindlin-Butler (4) technique was used for the determination. Exactly 15 seconds after the dye solution was added to the metaphosphoric acid filtrate, the galvanometer reading of the photoelectric colorimeter[3] was recorded. A crystal of vitamin C was added to decolorize the excess dye. The galvanometer was again read and if this reading were less than 100, the first reading was corrected logarithmically.

In a few cases, blood samples were taken from male interns who were on the same diet as the nurses.

RESULTS

The fasting vitamin C levels in the blood of 4 of the subjects during the menstrual cycle are shown in the curves of figure 1. The blood from 8 different women was analyzed for vitamin C but in only 3 cases were studies made for more than a single cycle. Four of the 8 women showed peaks in the level of the plasma vitamin C as early as the 13th and as late as the 18th day before the start of the next cycle (the actual dates were 13, 14, 14, 15, 17 and 18 days). Subjects *M.C.*, *E.M.* and *M.F.* had cycles of fairly regular lengths and in them the peaks occurred on the 14th, 15th and 16th day, respectively (fig. 1). Three of the 4 women who showed peaks in the level of plasma vitamin C

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[3] An Evelyn photoelectric colorimeter was used in these analyses.

later became pregnant; the fourth subject was unmarried.

The curves for the level of plasma vitamin C in the other 4 women were similar to those of *E.R.* and *M.H.* (fig. 1). None of these women has been pregnant. All of the male interns showed a fairly constant level of vitamin C in the plasma over periods comparable to those used in the above studies.

but it increased on the days corresponding to the peak in the plasma vitamin C level.

DISCUSSION

Too much significance can not be attached to the increased vitamin C level in the plasma of women during the middle of the menstrual cycle because of the few cases in our series. There is, however, much suggestive evidence

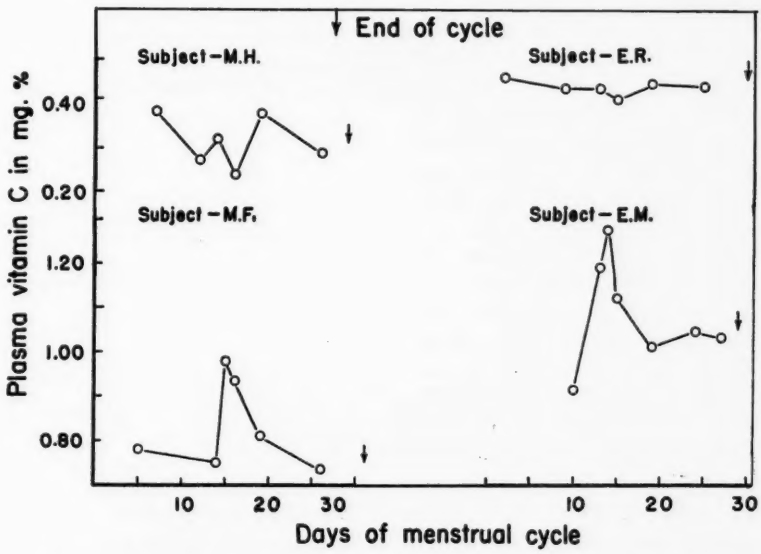

FIG. 1. Variations in fasting plasma vitamin C levels during the menstrual cycle.

Many of the blood samples which contained the increased amount of vitamin C were slightly hemolyzed. The presence of hemoglobin was verified by spectroscopic observation of the bands of the pyridine hemochromogen of hemoglobin. This hemolysis was not apparent in the samples taken at other times during the cycle nor in samples collected from other women on the same morning. All samples were collected under conditions which should reduce hemolysis to a minimum.

Subject *E.M.* was kept on a constant vitamin C intake during one menstrual cycle. Twenty-four-hour urine specimens were collected from the 10th to the 18th day in bottles containing sulfuric acid and 8-hydroxyquinoline as preservative (5). There was a slight fluctuation in the daily vitamin C excretion, that vitamin C may be associated with the reproductive process.

Robson (6) reviewed the evidence for the time of ovulation in women and concluded that in a 28-day cycle, ovulation may occur sometime between the 8th and the 23rd day with the greatest frequency in the middle of the cycle. The peaks in the plasma vitamin C levels in our series occurred during this same period.

Ovarian tissue has been shown to contain a high concentration of vitamin C. Analyses in our laboratory indicated that the cortex of the ovary contained as much as 50 mg. per cent of ascorbic acid while the medulla contained 25 mg. per cent. With the exception of the adrenals and the pituitary, there is no organ in the body which has as high a concentration of vitamin C as the ovary (7, 8). The ejaculate

from men also contains a high concentration of vitamin C (9). The follicular fluid secured from cases of ovarian cysts, on the other hand, contained less than 0.75 mg. per cent of vitamin C and so the concentration approached that in the plasma.

Sutton, *et al.* (3) showed that the injection of diethystilbestrol into female rats produced an increased excretion of vitamin C. Di Cio and Schteingart (10) found that when both vitamin C and gonadotropic hormone were injected into young rats, the increase in the weight of the testes or of the female reproductive tract was greater than when the hormone alone was injected. Israel and Meranze (11) found that vitamin C had a progesterone-like effect on the endometrium of young rabbits which had been primed by daily injections of estrogen.

In spite of all this suggestive evidence of a relation between vitamin C and the physiology of the reproductive tract, there is still no direct evidence for a specific or even indirect participation of vitamin C in this process.

In addition to the change in the plasma level of vitamin C which occurred in the middle of the menstrual cycle in 4 of the 8 women studied, there was evidence of a slight hemolysis in the blood drawn from the women during the peak of the plasma vitamin C. This hemolysis occurred only during the mid-part of the cycle. This slight hemolysis (the plasma appeared to contain a dark yellow pigment on these occasions) tended to decrease the plasma vitamin C level because of the interaction between hemoglobin and the vitamin (12). If this hemolysis could be prevented, the increase in the plasma vitamin C would be still greater.

One of the subjects developed a severe cold and a slight fever during the middle of one cycle. On this occasion the plasma vitamin C curve dropped sharply instead of showing a rise as it did the preceding month.

SUMMARY

A sharp increase in the fasting level of plasma vitamin C has been found in some women during the middle of the menstrual cycle.

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Relationship of the Adrenal Cortex to the Metabolism of Fat

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THE purpose of this paper is to review the experimental and clinical observations on the relationship of the adrenal cortex to the metabolism of fat and to consider the question: What is the rôle of adrenal cortical hormones in the etiology of the obesity which occurs in some patients having tumors or hyperplasia of the adrenal cortex?

Experimental Studies

Absorption. Verzar and his co-workers (1, 2) have reported a decrease from normal in the rate of fat absorption from the intestinal tract in adrenalectomized animals. They believe that this change is due to a decreased phosphorylation of fat in the intestinal mucosa. This problem has now been investigated in a number of other laboratories and it can be stated with reasonable certainty that Verzar's hypothesis regarding the rôle of the adrenal cortex in the phosphorylation of fat has been disproven. Barnes, Wick, Miller and MacKay (3) found no change from normal in the rate of the intestinal absorption of fat in adrenalectomized rats maintained on a high sodium chloride intake. Clark and Wick (4) studied the excretion of fat in the stools of adrenalectomized rats maintained on a high sodium chloride intake and compared the excretion values for several days with those of sham-operated rats. No significant differences were observed. Miller, Barnes, Kass and Burr (5) found that adrenalectomized rats on a high sodium chloride intake absorbed both unaltered corn oil and the methyl esters of the fatty acids of corn oil at a normal rate up to 6 hours after feeding. Similar results were reported by Barnes, Miller and Burr (6). However, Bavetta, Hallmann, Deuel and Greeley (7) observed a 24 per cent average decrease from normal in the rate of absorption of hydrogenated cottonseed oil given adrenalectomized rats maintained on a high intake of sodium chloride. The rate of absorption of fat was restored to normal by treating the adrenalectomized rats with adrenal cortical extract. In seeking an explanation for the discrepancy between their own results and those of Bavetta, *et al.* (7), Barnes, Rusoff and Burr (8) studied the intestinal absorption of corn oil, olive oil, hydrogenated vegetable oil and mutton tallow. The intestinal absorption of these fats in adrenalectomized rats on a high intake of sodium chloride did not differ from normal except that when an emulsion of hydrogenated vegetable oil and skim milk was administered according to the procedure used by Bavetta, *et al.* (7) a subnormal rate of fat absorption was noted. This finding did not provide a satisfactory explanation for the differences in results obtained by the two groups of workers for in a later study Bavetta and Deuel (9) compared the absorption time of hydrogenated cottonseed oil, corn oil, tributyrin and sodium butyrate in normal and adrenalectomized rats. The adrenalectomized animals were maintained on a high sodium chloride intake. The length of the absorption period and the dose of fat were identical with those employed by Barnes, *et al.* (8). Inhibition of absorption of both hydrogenated cottonseed oil and corn oil was noted in the adrenalectomized animals but the absorption of tributyrin and sodium butyrate did not change from normal. It was pointed out by

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Bavetta and Deuel that a probable cause of the lack of agreement in results was the difference in the age of rats used by the two groups of investigators. Barnes, *et al.*, used adult rats whereas Bavetta and Deuel used rats of 110 gm. in weight. It should be noted that the studies of Bavetta and co-workers did not provide any evidence that the subnormal rate of fat absorption in adrenalectomized animals was due to failure in phosphorylation processes. A direct study of the phosphorylation of fat in the absence of the adrenal glands was carried out by Stillman, Entenman, Anderson and Chaikoff (10). Male rats of approximately 200 gm. in weight were used. Normal and adrenalectomized rats with and without a high intake of sodium chloride were studied. Radioactive phosphorus was used as a labeling agent to study the entrance of phosphorus into the phospholipid molecule. The incorporation of radioactive phosphorus into phospholipid occurred to the same extent in normal and adrenalectomized rats irrespective of whether the latter were in good condition (high intake of sodium chloride) or were in poor condition.

It is probable but not certain that the cortical hormones have no specific effect upon the intestinal absorption of fat and that the slower-than-normal rate of absorption which characterizes cortical insufficiency is due to secondary changes.

Transport and storage. Harrop and Weinstein (11) found no consistent changes of the phospholipids in the blood of adrenalectomized dogs. The values were sometimes low and sometimes normal. A number of workers have reported an increase in the cholesterol of the blood in adrenalectomized animals and Villela observed (12) that the administration of 11-desoxycorticosterone acetate to normal guinea pigs depressed the level of cholesterol in the blood. Blanchard (13) found that in adrenalectomized cats the proportion of cholesterol in the red cells to that in the plasma was increased over normal and suggested that the permeability of the cell membrane was altered. Yeakel and Blanchard (14) found that in adrenalectomized cats following withdrawal of adrenal cortical extract there was a decrease in both phospholipids and total fatty acids in the blood plasma. There were smaller losses by the blood cells. The losses could not be accounted for but the suggestion was made that the fats may have penetrated the cells of the tissues.

In normal rats fatty livers can be produced by various methods but in adrenalectomized rats the deposition of fat in the liver is inhibited. Verzar and Laszt (15) noted that the fatty livers normally produced by phosphorus poisoning do not occur following adrenalectomy unless the animal is treated with cortin. MacKay and Barnes (16) and Fry (17) similarly observed that adrenalectomized rats do not develop fatty livers following the administration of anterior pituitary extract. MacKay (18) extended these observations and showed that adrenalectomy in the rat reduces the amount of fat deposited in the liver following the feeding of cream or pure fat, also during an alkalosis produced by feeding sodium bicarbonate or as a result of epinephrine injections. The high concentration of fat in the livers of rats, which previously received a diet high in fat, became reduced more rapidly in adrenalectomized animals than in the controls. Normally the female rat has more liver fat than does the male. Adrenalectomy tends to abolish this difference. MacKay and Carne (19) studied the level of fat in regenerating liver following partial hepatectomy and found that the remaining liver tissue becomes very fatty during 24 hours of fasting. The extent of fat deposition is decreased by adrenalectomy. Barnes, Miller and Burr (20) studied the transport of fat into the liver in the presence and in the absence of the adrenal glands. Adrenalectomized rats maintained on a high sodium chloride intake failed to deposit as much fat in the liver as did normal animals. The difference was due entirely to the reduced amount of neutral fat, whereas the phospholipid content of the livers of adrenalectomized animals was at a normal level, thereby indicating that a failure in the phosphorylation of fat did not occur. The failure in neutral fat transport to the liver was restored to normal by the administration of adrenal cortical extracts.

There is little information on the relationship of the adrenal cortex to the deposition of fat in tissues other than the liver. Adrenalectomized animals lose their body fat but this is probably due to the reduced intake of food.

When adrenalectomized rats or dogs are maintained on a high sodium chloride intake the body weight is well maintained but there have been no studies on the body fat of these animals. Ingle, Ginther and Nezamis (21) found that adrenalectomized rats maintained on a high intake of sodium chloride grew less well on a high fat diet than on a high protein, high carbohydrate or mixed diet. Bomskov and Schneider (22) have made the remarkable claim that adrenalectomized rats which survive due to compensatory hypertrophy of accessory adrenals may develop into giant rats with a weight 50 per cent above normal due to excessive deposition of fat. Goldzieher (23) has claimed that an extract of adrenal glands prepared by him had the effect of causing the fixation of blood fat in the tissues. Extracts prepared by the method described by Goldzieher are not recognized as possessing adrenal cortical activity. Adler (24), McKinley and Fisher (24) and Fieschi (25) claimed that their experimental animals gained in weight when fed dried adrenal cortex tissue. Such preparations are known to be without adrenal cortical activity. As yet there are no studies on the effect of the pure adrenal steroids on storage of fat. Corticosterone, 11-dehydrocorticosterone, 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone are each capable of causing normal rats to lose weight when large amounts are administered. Body fats have not been studied in such experiments. Thus far no investigator has reported the production of obesity in an experimental animal treated with a pure adrenal steroid.

The available experimental data show that in adrenalectomized animals fatty livers are produced much less readily if at all by any of the experimental methods used. This is probably due to faulty deposition of fat in the liver although inadequate mobilization of dépot fat or a high rate of removal of fat from the liver might be listed as possible factors. In adrenalectomized animals there is also a failure of the liver to form urea, ketones and glucose and to deposit glycogen at normal rates. How are these deficiencies related to the faulty deposition of fat? A number of investigators believe that the failure in deposition of fat is one of the primary changes of cortical insufficiency for the reason that it persists in adrenalectomized animals maintained in a state of apparent good health on a high intake of sodium chloride. The reviewer does not believe that the relationships of the deficiency in deposition of liver fat to the primary and secondary changes of cortical insufficiency have been established.

Intermediary fat metabolism and oxidation. It is now generally accepted that the formation and oxidation of ketone bodies is an important phase of the metabolism of fat. The liver is probably the only site of their formation. Ketone bodies are burned in the peripheral tissues but do not account for all the oxidation of fats. Increased ketosis is usually associated with some degree of decrease in carbohydrate oxidation, such as occurs during starvation or diabetes, and probably represents a compensatory response. The relative importance of increased production and of under-utilization of ketone bodies in causing ketonemia and ketonuria is not agreed upon by all workers in the field.

Long and Lukens (27) reported that adrenalectomy produced a marked reduction in the ketone-body excretion of the depancreatized cat. Burn and Ling (28) demonstrated that extracts of the anterior pituitary were ketogenic. Steppuhn (29) suggested that the ketogenic effect of anterior pituitary extracts was mediated by the adrenal cortex. Long (30) showed that the ketonuria caused by anterior pituitary extracts was abolished by adrenalectomy. Fry (17) administered anterior pituitary extracts to normal and adrenalectomized rats and found that in the absence of the adrenal glands ketonuria did not occur. Adrenalectomized rats maintained in good condition by either a high intake of sodium chloride or of adrenal cortex failed to develop ketonuria following the administration of anterior pituitary extracts. It is now recognized that although small doses of adrenal cortical extracts will maintain life and growth in adrenalectomized animals much larger amounts are required to maintain the normality of all metabolic processes.

The effect of adrenalectomy in decreasing or abolishing the ketonuria induced by anterior pituitary extracts has been confirmed by MacKay and Barnes (31), Mirsky (32), Neufeld

and Collip (33), Shipley (34), MacKay and Wick (35) and other workers. Evans (36) observed that adrenalectomy in the rat reduced the ketonuria of phlorhizin diabetes. MacKay and Barnes (37) found that the female rat exhibits a greater ketonuria than the male following the administration of ketone bodies or higher fatty acids and that this sex difference was abolished by adrenalectomy. Also, MacKay and Barnes (38) have shown that the ketonuria produced by feeding the sodium salts of diacetic or beta-hydroxybutyric acid to fasting rats is reduced by adrenalectomy. The significance of the effect of adrenalectomy upon experimentally induced ketonuria in the rat was brought into question by the studies of MacKay and Wick (35), Mirsky (32) and Neufeld and Collip (33) which indicated that there was an increase in the kidney threshold for the excretion of ketone bodies following adrenalectomy and that an increase in ketonemia still occurred in the absence of the adrenal glands. From these results it would appear that the extent of ketonuria is not a reliable index of the extent of ketosis. Shipley (34) studied the blood thresholds at which normal and adrenalectomized rats excreted ketone bodies in the urine following administration of anterior pituitary extracts. He found no evidence for the existence of an elevated renal threshold for ketone bodies in adrenalectomized rats. The adrenalectomized rats maintained on a high sodium chloride intake showed some hyperketonemia and ketonuria when anterior pituitary extracts were administered but the response was less than normal.

Shipley and Fry (39) studied the effect of corticosterone, 17-hydroxy-11-dehydrocorticosterone, 11-desoxycorticosterone, adrenal cortical extract and anterior pituitary extract on ketosis in the rat. In these experiments the ketone level of the blood was determined 4 hours after the test substance was administered. Only the anterior pituitary extracts caused ketonemia to occur by this time. This fact provides a differentiation between the action of adrenal and pituitary principles but it leaves open the question as to whether adrenal cortical hormones might induce a ketonemia after a longer latent period. Ingle and Thorn (40) observed that partially depancreatized rats made severely diabetic by the administration of 17-hydroxy-11-dehydrocorticosterone occasionally exhibited a severe ketonuria. But these observations are probably without special significance since rats under similar conditions made severely diabetic by any cause may exhibit ketonuria. A full evaluation of the significance of changes in the amounts of ketone bodies in the blood and urine would require accurate estimation of renal thresholds, rate of ketosis and rate of utilization. It has not yet been possible to evaluate all of these factors simultaneously.

Thorn and co-workers (41) have emphasized that patients having Addison's disease exhibit a high respiratory quotient thus indicating that the principle source of heat is carbohydrate. The respiratory quotient is lowered by the administration of adrenal cortical hormones thus providing evidence but not proof that more fat and less carbohydrate is being oxidized. If such changes in the proportion of fats and carbohydrates burned occur, is it primarily a matter of suppressing the oxidation of carbohydrate and does the compensatory increase in the burning of fat occur without being directly related to hormonal mechanisms or is the primary effect of the cortical hormone to stimulate the oxidation of fat? The manner in which the organism controls the balance between oxidation of the different food stuffs is not known. Samuels, Reinecke and Ball (42) have shown that the hypophysectomized rat can be adapted to a high fat diet so that it is no longer dependent upon exogenous carbohydrate to sustain a nearly normal blood sugar during fasting. It would be of interest to determine whether the adrenalectomized animal is also capable of becoming adapted to burning fat instead of carbohydrate.

Comment. The studies on fat metabolism in experimental animals have shown significant changes from normal especially in the deposition of fat in the liver and in the response to experimental conditions which induce ketonuria. But no proof exists that the hormones of the adrenal cortex exert a direct control upon the metabolism of fat. It is conceivable that all changes studied thus far are secondary to the more primary effects of the cortical hormones on the metabolism of carbohydrate and

on the distribution of water and electrolytes and other mechanisms involved in the circulation of blood and lymph. Many investigators are impressed by the state of apparent vigor and good health of the adrenalectomized rat maintained on a high sodium chloride intake and may not agree with the opinion of the reviewer that such animals maintain adequacy of the metabolic processes with difficulty and lack the capacity for normal adaptation to a change such as is required by those experimental conditions which cause fatty livers or by the administration of ketogenic agents. It must be admitted that the use of such terms as primary and secondary factors in adrenal insufficiency represents a retreat to generalities and that attempts to maintain a distinction between primary and secondary changes can easily be carried to absurdities. But until the cycle of changes instigated by removal of the adrenal cortices can be described in full it will serve a useful purpose to try to discriminate between effects which appear to concern the metabolic processes directly and those due secondarily to a decay in the supporting mechanisms.

It has not yet been shown that the administration of adrenal cortical hormones alters the metabolism of fat in non-adrenalectomized animals whereas the cortical hormones do alter the metabolism of carbohydrate and electrolytes in non-adrenalectomized animals. The existence of over-dosage effects which are in the direction opposite to those of deficiency states is to be expected if the relationship between hormone action and physiologic response is direct.

Clinical Observations

Addison's disease is generally characterized by a loss of body weight although a few patients having the disease are obese and others appear to have preserved their deposits of fat despite a loss of weight. A decrease in the intake of food is probably the major cause of the loss of weight. Gains in weight are usually seen when adequate therapy is instituted. Patients having Addison's disease have a high respiratory quotient (41) which suggests that the amount of fat oxidized is small. The administration of adrenal cortical extracts or of 17-hydroxy-11-dehydrocorticosterone (41) causes a fall in the respiratory quotient which suggests that the hormone may cause an increase in the oxidation of fat. Whether there is a direct effect of the cortical hormones on the oxidation of fat or whether an increase in the oxidation of fat is compensatory for a decrease in the oxidation of carbohydrate is not known with certainty.

The most important clinical manifestation of a relationship between the function of the adrenal cortex and the metabolism of fat is seen in some patients having adrenal cortical tumors or adrenal cortical hyperplasia. The typical syndrome includes virilism, hypertension, glycosuria, striae, osteoporosis and obesity. It is commonly termed Cushing's syndrome and has been distinguished (43) from the adrenogenital syndrome in which the changes are limited to a disorder of the sex characteristics. None of these symptoms is found to occur in all cases having cortical tumors or hyperplasia and there is not full agreement among clinicians on the signs of adrenal cortical dysfunction. It is known that some tumors of the adrenal cortex do not cause symptoms and that these same symptoms may be associated with basophilic adenomas of the pituitary and with tumors of the thymus and pineal glands.

Lukens, Flippin and Thigpin (44) reviewed 55 proven cases of tumor or hyperplasia of the adrenal cortex and found that obesity occurred in 49 per cent of the group. The obesity is frequently of the 'buffalo' type in which the deposition of excess fat is confined to the neck, face and trunk and the extremities remain thin. It should be emphasized that in some patients the obesity is generalized, other patients do not become obese and an occasional patient may be emaciated when all other signs of cortical hyperfunction are present. Marks, Thomas and Warkany (45) have reviewed 24 cases of obesity associated with tumors of the adrenal cortex in children. In some of the group the obesity was generalized rather than of the 'buffalo' type and the authors indicate that in spite of the obesity the actual weight of the children was not always much greater than average. Kepler and Keating (46) have pointed out that the most characteristic change is not the over-all gain in weight but the full-

ness of the face and neck which may co-exist with an actual loss in body weight in severe cases (47).

Patients having obesity associated with cortical tumors or hyperplasia have not been thoroughly studied from the standpoint of evaluating changes in the metabolism of fat. In studying the literature on the subject the reviewer was impressed by the lack of data on this aspect of the syndrome. Little information is given about the nature and distribution of fat in the autopsy reports. Freyberg and Newburgh (48) have reported a detailed study of obesity and energy exchange in a single case of pituitary basophilism without cortical tumor or hyperplasia. It was demonstrated that the energy exchange was normal and that obesity was not the result of any unusual metabolic feature. It was concluded that the patient became obese because the intake of energy exceeded the expenditure of energy; the excess energy being stored as fat. It was noted by Lukens, Flippin and Thigpin (44) that in a case of a woman with an adrenal cortical adenoma with absence of the opposite adrenal there was massive adipose deposition in the viscera and that the liver fatty acids were 35 mg. per cent whereas the normal range is 2 to 5 mg. per cent.

Do these patients become obese because of some secondary change in ratio between caloric intake and caloric output or is there some direct hormonal effect upon the formation, transport and storage of fat? The fact that many of these patients develop the peculiar 'buffalo' type of obesity in association with other signs of hypercortico-suprarenalism and that it disappears in those patients who survive the complete removal of adrenal cortical tumors is the best evidence that the cause of the obesity lies in the adrenal cortex.

The nature of the hormonal imbalance which is thought to cause the signs of hypercortico-suprarenalism is obscure. In those cases having pathologic changes in the adrenal cortices, tumors or hyperplasia, it is assumed that excessive amounts of the cortical hormones are produced and that these cause the symptoms. But an identical or at least a very similar syndrome is associated with basophilic adenomas of the pituitary body and with tumors of the thymus and pineal glands. Since neither the pineal nor thymus glands are known to have any endocrine function attention is generally directed to either the pituitary or the adrenal glands in an effort to find a common denominator causing the syndrome. Crooke (49) has claimed that all cases having Cushing's syndrome show hyaline changes in the basophilic cells of the anterior lobe of the pituitary even when there are coexisting neoplasms of the thymus or the adrenal cortex. Other investigators, particularly Broster and Vines (50) have emphasized the importance of adrenal cortical hyper-activity in all of those cases which exhibit virilism. They claim that the adrenal cortex may be abnormally active even though it is apparently normal in size and that the state of hyperactivity can be detected by the Poinceau-fuchsin staining reaction of the cortex. At present there is no general agreement among workers in the field as to whether dysfunction of either the pituitary or the adrenal glands is always involved in Cushing's syndrome.

In respect to tumors of the adrenal cortex there are good reasons for believing that they secrete some of the cortical hormones in abnormally large amounts. As Kepler (51) has indicated, adenomas of the thyroid and parathyroid glands, the islands of Langerhans, the testes and ovaries may manifest functional potentialities and in some cases function in excess of the physiologic needs of the organism. In the case of adrenal cortical tumors there may be compensatory atrophy of the contralateral adrenal cortex which is evidence of an excessive production of the cortical hormones. The successful surgical removal of the tumor is always followed by disappearance of the symptoms unless metastases or recurrence takes place.

In regard to patients having hyperplastic adrenal cortices there are a number of reports, many uncritical and unconvincing, of clinical improvement following resection of the glands. From one point of view there is the same rationale for partial ablation of hyperplastic cortical tissue as exists for partial thyroidectomy in patients having hyperthyroidism. But the fact that in experimental animals the adrenal cortices hypertrophy in any disease or

other form of stress to which the animal may be subjected and that this hypertrophy is apparently compensatory and suffices only to meet the increased physiologic needs for cortical hormone, raises the question as to how the surgeon finding enlarged adrenal glands in a patient can know that the hypertrophy is pathologic and not compensatory. If the hypertrophy causes, and is not the result of, altered physiologic processes in the body this poses an interesting question to the clinical physiologist. What is the mechanism by which the adrenal cortex is stimulated to secrete excessive amounts of its hormones? Is the stimulation by means of the adrenotropic hormone of the anterior pituitary and is a dysfunction of the pituitary primary to adrenal cortical dysfunction, or can other abnormal stimuli arising either within or extraneous to the adrenal cortex cause hyperactivity without involvement of the pituitary gland?

In considering the possible hormonal changes in patients having hyperplastic adrenal cortices it is interesting to note the remarkable case of Wilkins, Fleischman and Howard (52), that of a young boy having coexisting Addison's disease and macrogenitosomia who at autopsy was found to have adrenal hyperplasia. They suggested that the hyperplastic cortices secreted abnormally large amounts of androgens and failed to produce normal amounts of those steroids essential for life.

When the known hormones of the adrenal cortex and their overdosage effects in experimental animals are considered it is possible to explain several of the principal symptoms of Cushing's syndrome by assuming them to be due to hypercortico-suprarenalism. The blood pressure of normal experimental animals can be raised by the administration of 11-desoxycorticosterone (53). This effect has also been frequently observed in the patient. Ingle (54, 55) has induced severe diabetes in rats by means of 17-hydroxycorticosterone and 17-hydroxy-11-dehydrocorticosterone. Thorn and Clinton (56) and Kepler (57) have independently demonstrated the diabetogenic action of adrenal steroids in patients having coexisting Addison's disease and diabetes. Virilism may be due to the secretion of androgens by the adrenal cortex. Reichstein (58, 59) has isolated adrenosterone and 3,11-dihydroxyandrostane-17-one, both androgenic, steroids, from beef adrenal glands. Palmer and de Ronde (60) have reported on the production of virilism in women by the administration of testosterone.

The occurrence of obesity, striae and osteoporosis in patients having Cushing's syndrome has no parallel in the experimental observations on the biologic effects of the adrenal steroids. Albright, Parson and Bloomberg (61) have presented an exceedingly interesting hypothesis which conceives of Cushing's syndrome as hyperadrenocorticism leading to increased gluconeogenesis from protein so that a protein deficiency results. Studies (62) on the excretion of the 17-ketosteroids provide evidence of increased production of steroids by the adrenal cortex in cases of Cushing's syndrome. The metabolic data indicate an abnormally high rate of protein catabolism. The osteoporosis is considered to result from a failure to lay down bone matrix due to the disordered protein metabolism, the obesity to a conversion to fat of the increased amount of glucose derived from protein and the so-called girdle obesity is thought to be due in part to a weakened and relaxed abdominal wall.

This stimulating hypothesis should be considered in the same conservative spirit as it was presented by Albright and his colleagues. It has the advantage of explaining the principal symptoms of Cushing's syndrome in terms of the known properties of the cortical hormones. The therapy applied to correct the principal metabolic change assumed by the hypothesis, that of excessive protein catabolism, has resulted in the clinical improvement of patients having Cushing's syndrome. But the hypothesis has not yet been established and other explanations of the known facts are possible. To the reviewer the following points seem to deserve consideration. Recent studies on the influence of the C_{11} oxygenated cortical steroids show that their property of stimulating protein catabolism is overshadowed by their inhibitory effect on the peripheral utilization of carbohydrate. Hypergluconeogenesis alone will not explain the production of adrenal steroid diabetes. There is evidence that animals and patients treated with these compounds utilize

more fat, which might be expected to prevent the storage of fat. Ingle and Evans (55) have shown that the administration of either 17-hydroxycorticosterone or 17-hydroxy-11-dehydrocorticosterone to normal rats caused only a temporary period of negative nitrogen balance during which the animal lost weight without an increased storage of fat. Adaptation occurred so that the nitrogen balance again became positive. It is quite possible that adaptation to an excess of the C_{11} oxygenated steroids would occur less readily in the human being than in the rat. It was also noted by Ingle and Evans (55) that the maximum excretion of nitrogen that could be induced in the rat by means of the C_{11} oxygenated steroids was not greater than the amounts of nitrogen excreted by partially depancreatized rats having diabetes. In many human diseases, for example untreated diabetes, there is an excessive catabolism of protein. Are there any examples of other diseases causing protein deficiency which result in symptoms similar to those occurring in Cushing's syndrome?

Cushing (63) expressed the opinion that the obesity of Cushing's syndrome was due to a disturbance in the tuber-hypophyseal mechanism. Experimentally induced hypothalamic lesions may cause obesity in animals (64).

Comment. The subject of obesity, irrespective of the cause, is poorly understood. In considering the relationship of obesity to a dyscrinism it must be kept in mind that obesity occurs in large numbers of individuals without disease and that to a certain extent may be associated with the disease in question by chance alone.

Although many of the patients having Cushing's syndrome associated with adrenal cortical tumor or hyperplasia have been described as obese this is not a constant symptom and a still smaller number of patients show the buffalo type of obesity. As Albright and his colleagues have pointed out, the so-called girdle obesity, in some patients at least, may be more apparent than real. As far as the fullness of the neck and face is concerned there is nothing in the literature to show that this is due to an accumulation of fat rather than of intracellular fluid. However, Dr. H. E. Robertson, Department of Pathology, The Mayo Clinic, is able to confirm for the reviewer the fact that the fat which accumulates as the result of adrenal cortical tumors is a true adipose connective tissue and is not due to an increase in tissue fluids.

The balance between energy intake and output has not been evaluated in any of the cases having adrenal cortical tumor or hyperplasia. In the one case of Cushing's disease investigated by Freyberg and Newburgh (48) it was shown that the obesity probably resulted from an excessive caloric intake. In patients having debilitating diseases without digestive disorders it seems reasonable that a reduction in caloric output without a comparable reduction in caloric intake would favor the storage of fat. Only the hypothesis of Albright and his colleagues that the hypergluconeogenesis from protein with conversion to and storage as fat is caused by an increase in the secretion of the C_{11} oxygenated steroids, explains the obesity of Cushing's syndrome in terms of the known properties of adrenal cortical hormones.

Metabolic studies on patients having obesity associated with hypercortico-suprarenalism would aid greatly in elucidating this interesting problem of clinical physiology. This review of the subject will serve a useful purpose only if it contains proper emphasis on the unsatisfactory nature of the available data and has the effect of stimulating more objective studies on the problem.

SUMMARY

In laboratory animals, adrenal cortical insufficiency is characterized by a slower-than-normal rate of absorption of fat, a decrease in the amount of fat transported to and deposited in the liver under conditions which normally cause fatty livers, a smaller-than-normal response to ketogenic agents and by a normal or high respiratory quotient. It is not known to what extent these changes are primary in nature and to what extent they are secondary to failures in functions more directly controlled by the cortical hormones. No overdosage effects of the cortical hormones upon these phases of fat metabolism have been noted except for a depression of the respiratory quotient which may indicate that an increase in the oxidation of fat has occurred.

Patients having adrenal cortical tumors or hyperplasia are frequently obese but this symptom is not always present. Although some of the changes from normal in patients having hypercortico-suprarenalism can be explained in terms of the known properties of adrenal cortical hormones, the rôle of the cortical hormones in the etiology of obesity remains in doubt.

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COMMUNICATIONS

TESTOSTERONE OINTMENT THERAPY IN A 6-MONTH-OLD BABY WITH SEVERE GENITAL RETARDATION

IT WOULD seem obvious that testosterone compounds administered as an inunction, if effective, would constitute a more desirable and convenient method of treating infants, than when given parenterally, perorally, by implantation, or sublingually. Herewith follows a brief case report, with photographs, to illustrate the above contention.

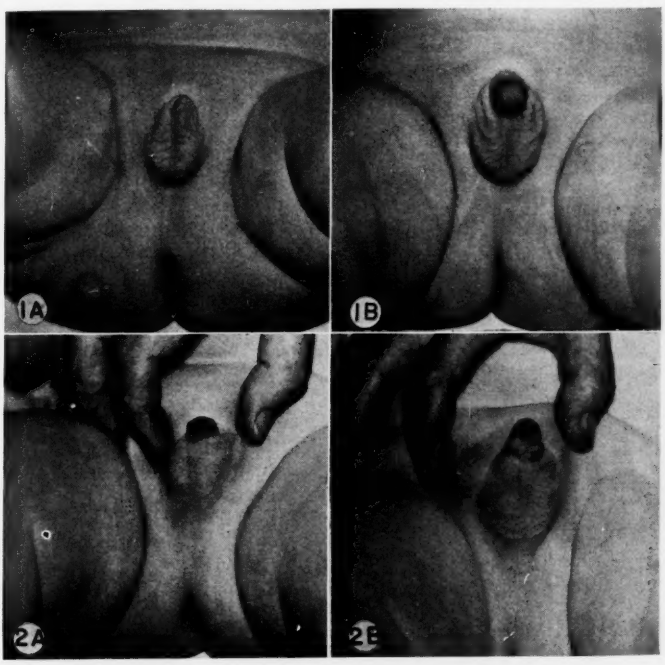

FIG. 1a. *Baby R. F.*, May 27, 1943, age 6.5 months; 1b. Sept 20, 1943, age 10.5 months. Methyl testosterone inunctions nightly during above four months; no other treatment.

FIG. 2a. *Baby R. F.*, May 27, 1943, age 6.5 months; 2b, Sept. 20, 1943, age 10.5 months. Methyl testosterone inunctions nightly during above 4 months; no other treatment.

Baby R. F., was referred by Dr. J. C. Parrott of San Francisco, and was first seen on May 12, 1943, when lacking 2 days of being 6 months old. The sole complaint was undeveloped genitalia.

The mother knew of no endocrinopathies on either side of the family, although she herself had not begun to menstruate until 15 years of age, and the intervals between periods varied, sometimes being a month late.

The baby was born rapidly during a brief 2.5-hour labor, head first, without instruments; birth weight was 8 lb. 5 oz.; it was thought that the birth occurred about 3 weeks past full term. During the succeeding 6 months the baby grew normally, slept well and was a very lively happy child. No teeth had erupted.

Apparently nothing unusual regarding the genitalia was noted at birth, although the mother considered the penis to be very tiny when the child was 3 weeks of age. As the baby became fatter the penis was no longer visible. One testis was reported as normal, the other "underdeveloped."

At 6 months the baby's height was 26.5 inches, the range of normal heights being 23 to 30 inches. He

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weighed 19 lb., the supposed ideal weight for height and age being 17.5 lb. The child's appearance was quite normal and radiantly healthy. The bridge of the nose was slightly flat but there was no protrusion of the tongue.

The penis was not visible until the mons veneris fat pad was pushed back; it then came into view, the penis being exceedingly tiny but normally formed (fig. 1a and 2a). The left testis was palpable, the size of a petit pois; the right testis was not felt with certainty.

Roentgenogram of the skull revealed no abnormalities; the sella turcica was of normal size and shape. Roentgenograms for determination of bone age were estimated at 18 months.

Male hormone ointment[1] was prescribed in a strength of 2 mg. of methyl testosterone per gm. of ointment, 25 gm. of inunction material per tube of ointment. The mother was instructed to massage gently 1 cm. of ointment, as expressed from the tube, for 5 minutes into the skin of the abdomen, back or thighs, each night, and permit to remain overnight without cleansing.

[1] The testosterone ointment used (Oreton-M) was furnished by The Schering Corporation of Bloomfield, New Jersey.

This treatment was started on May 12, 1943; unfortunately arrangements for photographs were delayed until May 27, by which time the mother reported that the penis was already constantly visible; even so figures 1a and 2a show the diminutive genital status. Improvement was prompt, remarkable and progressive.

By Sept. 20, 1943, about 4 months later, the genital status was considered to be normal (fig. 1b and 2b), and treatment was discontinued. No regresssion had occurred when the child was seen a month later. Both testes could be readily felt in the scrotum. The child had been walking for the past month and a half, and by 11 months of age 3 teeth had erupted. The hormone therapy had not caused any noticeable irritability. The child's behavior continued to be happily normal.

Summary. The case is reported of a male infant whose genital development was strikingly subnormal. Coincident with androgen treatment by inunctions marked genital enlargement ensued.

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DESOXYCORTICOSTERONE ACETATE AND WATER EXCHANGE

Recently, several investigators (1,2) have reported the effect of desoxycorticosterone acetate on the water balance of the body. This substance, as well as certain other adrenal cortical steroids, appears to produce an increased water intake and output. It has been suggested that this is a 'diabetes-insipidus'-like polyuria. However, the posterior pituitary anti-diuretic principle has little or no effect upon polyuria so induced.

The explanation of the mechanism of the polyuria induced by desoxycorticosterone acetate is not as yet entirely clear. There appear to be four major physiologic changes associated with the administration of desoxycorticosterone acetate that may contribute to the production of the increased water exchange. These changes are primarily an effect upon *a*) the kidney; *b*) the circulatory volume and interstitial volume; *c*) the tissue cells generally, particularly muscle tissue; and *d*) the concentration of sodium in the fluid of the extracellular space. All of these changes are inter-related. One, however, may play the predominant rôle in producing a state whereby an increased water exchange is maintained.

In regard to the kidney, it appears that desoxycorticosterone acetate acts primarily on the kidney tubule enhancing the excretion of potassium and the reabsorption or retention of sodium (3,4). In addition, the prolonged administration of desoxycorticosterone acetate produces an increase in the weight of the kidneys and the size of the renal tubules which may contribute to the production of a polyuria (5,6). The effect of desoxycorticosterone acetate on the circulating volume and the volume of the extracellular fluid has been described by several workers (7). There appears to be an increase in the extracellular volume and the plasma volume after prolonged administration of desoxycorticosterone acetate. This possibly would increase the rate of urine formation by providing a larger volume of water available for excretion. Prolonged administration of desoxycorticosterone acetate also produces a partial replacement of cellular postassium by sodium (8). There does not appear to be, however, any significant change in the water content or volume of the cell associated with this change. The effect of the replacement of potassium by sodium *per se* on the water exchange of the body is not known. Low potassium states in man and experimental animals such as in adrenal hyperfunction or familial periodic paralysis do not seem to be associated with unusual polyuria. Finally, several investigators have recently suggested that the polydipsia and polyuria produced by desoxycorticosterone acetate are due primarily to the slight elevation of plasma sodium (2,9). The increased water exchange appears to be secondary to the increased salt retention, as a necessary measure for the maintenance of a proper osmotic pressure relationship.

Each of these above mechanisms is necessarily interrelated. The disturbance in the kidney threshold for the excretion of sodium forcing its retention without adequate associated retention of water, would create a physiologic stimulus for an increased water intake. This effect may be primary. A change in the selective preference of the muscle and other cell membranes for certain electrolytes may also contribute to this increased water appetite. This change in threshold for the excretion of sodium and potassium may be followed by several compensatory responses. These are all designed to maintain a normal osmotic pressure relationship of the body. The increase in the extracellular and plasma volume, the partial replacement of tissue potassium by sodium, the increased water appetite, may all be compensatory mechanisms adapted to restoring the composition of the extracellular fluid to a normal state. The general effect of desoxycorticosterone acetate on tissue permeability is not to be disregarded, however.

The use of desoxycorticosterone acetate in certain clinical states in which an increase in water exchange would be highly desirable has not been extensively tried (10). The ability of desoxycorticosterone acetate to prevent experimentally induced water intoxication in animals, and to modify pitressin-induced convulsions in man, suggests its clinical use. Such a procedure is certainly not without danger. In experimental animals the partial depletion of intracellular potassium by the prolonged administration of desoxycorticosterone acetate is associated with such severe disturbances in cellular metabolism that muscle weakness and paralysis have been described.

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Abstracts of CURRENT ENDOCRINE LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. DONALDSON, J. W. EVERETT, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, HANS O. HATERIUS, CHARLES W. HOOKER, R. G. HOSKINS, J. E. HOWARD, J. T. LEWIS, T. H. MCGAVACK, A. E. MEYER, MARY L. MILLER, C. C. PFEIFFER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., BORIS B. RUBENSTEIN, PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, EMMERICH VON HAAM, HAROLD WOOSTER.

ADRENALS

CLEVELAND, M., AND LEILA C. KNOX.

Bilateral carcinoma of the adrenal cortex with metastasis to the iliac bone. *Arch. Surg.* 47: 192. 1943.

A case of bilateral carcinoma of the adrenal cortex with metastasis to the right iliac bone is presented. The patient, a 57-year-old white male, presented the classic signs of insufficiency of the adrenal cortex. There were no sexual abnormalities, such as have been reported in other patients with similar lesions. Following an extremely simple operative procedure (removal of a specimen of the bone tumor for diagnosis) the patient collapsed completely and died on the second postoperative day. At autopsy, no normal adrenal tissue was found. The only secondary tumor was that in the iliac bone. Forty-nine cases of adrenal tumors were collected from the literature and reviewed. The tumors were bilateral in only five cases.—*D.P.*

DUNLOP, D.M.

Desoxycorticosterone in Addison's disease. A comparison of different methods of administration. *Brit. Med. J.* 1: 557. (May 8) 1943.

This paper deals with the relative effectiveness of desoxycorticosterone acetate when absorbed from the buccal cavity in comparison with its potency when administered by implantation or intramuscular injection. Seven patients suffering from characteristic and unequivocal Addison's disease were studied. Doca proved effective in 2 cases of Addison's disease when administered sublingually dissolved in propylene glycol. The method proved cumbersome and wasteful. Doca was effective in 5 cases when administered sublabially in tablets. The method proved convenient but very wasteful. Three patients were treated by implantation of Doca. This mode of therapy proved the method of choice on the grounds of both economy and convenience. Intramuscular injection of Doca, though very effective proved less economical and much more inconvenient than implantation, and its use was reserved for initial control in untreated cases.—*R.B.G.*

HYMAN, H., AND W. H. MENCHER.

Pheochromocytoma of the adrenal gland. *J. Urol.* 49: 755. 1943.

Pheochromocytoma of the adrenal gland is a tumor of the medullary portion producing hormonal symptoms. This type of tumor produces surgically remediable form of paroxysmal hypertension, caused by prolonged excessive discharge of adrenalin into the general circulation. There have been 35 reported cases in the literature, 4 of which are given in this paper. Diagnosis is based on the typical symptomatology during an attack, the typical pressor response mechanisms, the demonstration by bio-assay of pressor substance in the blood of a patient during the height of an attack, and the demonstration of the tumor by perirenal insufflation. All of the tumors in the authors' series were removed successfully, and all patients made uneventful recoveries.—*H.W.*

LAWRENCE, R. D.

Gynaecomastia produced by desoxycorticosterone acetate (Doca). *Brit. Med. J.* 1: 12. (Jan. 2) 1943.

A brief case report is recorded in which enlargement of the male breasts occurred during treatment of Addison's disease with desoxycorticosterone actetate. When desoxycorticosterone acetate was stopped the mammary enlargement disappeared in spite of continuous large doses of eschatin.—*R.B.G.*

LAWSON, H. A., I. A. BECK, AND R. G. MURPHY.

Addison's disease: Report of a fatal case. *New Eng. J. Med.* 228: 480. (Apr. 15) 1943.

A case of rapidly fatal Addisonian crisis due to tuberculosis of the adrenal glands in a soldier on active duty is reported as noteworthy because of the complete absence of pathologic pigmentation, normal blood sugar and blood urea nitrogen and an ascertainable clinical history of only four weeks.—*R.B.G.*

PARKS, T. J.

Edema and toxemia of late pregnancy: the possible relation of the fetal adrenal glands to sodium and potassium imbalance. *M. Rec.* 156: 355. 1943.

The author suggests that the success of therapy of puerperal toxemia and eclampsia by reduction of sodium intake indicates that in the last trimester of pregnancy the surplus cortical secretion from the hypertrophied fetal adrenal glands, with a low potassium and high sodium intake, results in edema in the mother. Ample, though not entirely pertinent, references to the literature are given to support this hypothesis. The author's experimental evidence rests on the improvement of 39 edematous gravidae in the last trimester on a NaCl-poor diet with potassium chloride therapy.—*H.W.*

TALBOT, N. B., A. M. BUTLER, AND E. A. MACLACHLAN.

The effect of testosterone and allied compounds on the mineral, nitrogen, and carbohydrate metabolism of a girl with Addison's disease. *J. Clin. Invest.* 22: 583. 1943.

Under controlled hospital conditions and several types of hormonal therapy, variations in the body weight, nitrogen balance, carbohydrate metabolism, output of 17-ketosteroids, values for potassium in the blood and urine, and the excretion of sodium, chloride, creatine, creatinine, and total and urea nitrogen were observed over a period of 300 days in a girl of 8 years suffering from Addison's disease, moniliasis, and idiopathic hypoparathyroidism. Three milligrams of desoxycorticosterone acetate was given intramuscularly daily throughout a major portion of the experimental period. The diet contained 15 grams of sodium chloride and 6.4 grams of available nitrogen during the first 131 days and 9.8 grams of sodium chloride and 7.7 grams of nitrogen during the remainder of the period. Treatment directed to the management of the parathyroid condition was shown not to influence the factors studied in connection with her Addison's disease. Under these conditions, methyltestosterone in doses of 90 milligrams daily and testosterone propionate in doses of 25 to 50 milligrams daily, respectively, produced a gain in weight, a diminution in the urinary excretion of nitrogen, potassium and sodium, and a lowering in the concentration of serum potassium. When desoxycorticosterone acetate therapy was withdrawn, testosterone propionate in 50 mg. doses daily prevented the appearance of any of the signs or symptoms of acute adrenal insufficiency, whereas methyltestosterone was totally ineffective in this regard. Fasting blood sugar concentrations were not influenced by the use of testosterone, methyl testotsterone or methyl androstenediol. Methyl androstenediol, 90 mg. daily by injection, decreased the excretion of nitrogen in the urine, but did not favorably influence body weight.—*T.H.McG.*

TIMONEY, F. X.

Non-hormonal adrenal adenoma: case report. *J. Urol.* 49: 654. 1943.

This report is a description of a 4200 gm. benign adrenal adenoma removed from a 37 yr. old female patient. No hormonal assays are reported on the patient, but apparently no masculinization of the patient had occurred.—*H.W.*

ENDOCRINE GENERAL

BENDA, C. E., N. A. DAYTON AND RUTH A. PROUTY.

On the etiology and the prevention of mongolism. *Am. J. Psychiat.* 99: 822. 1943.

In a statistical study it was found that whereas most types of feeble-mindedness occur at random, as regards birth order, in mongolism the incidence is very high at or near the end of the birth series. This finding is interpreted as indicating that mongolism is due to an acquired disorder of the mother. The mongolism occurs mainly: (a) when the mother is approaching the menopause; (b) when the mother is immature or when the child is born after a long period of waiting; (c) in the middle of the childbearing period when extrinsic factors have intervened. The common denominator of these conditions is threshold sterility, usually due to endocrine deficiency. It is suggested that careful examinations of poten-

tial mothers with a view to detecting the ominous maternal condition might serve significantly to reduce the number of mongoloid births.—*R.G.H.*

DiMaio, M., and C. E. Bird.

Pellet implantation. *New Eng. J. Med.* 228: 390. (Mar. 25) 1943.

A simple, short operative technic is described for the implantation of pellets of hormone under the skin with the aid of a trochar and cannula. Implantations were performed in the operating room under the usual aseptic precautions. The infrascapular region was found to be best suited for pellet implantation.—*R.B.G.*

Foldes, F. F.

The prolongation of the action of subcutaneously injected medicines in man. *J. Clin. Invest.* 22: 499. 1943.

The precipitating action of zinc chloride in an alkaline medium was made the basis for determining its ability to decrease the absorption of drugs injected subcutaneously or intramuscularly. In concentration of from 0.06 to 0.1% it was found to (1) prolong the antidiuretic effect of posterior pituitary extract, (2) delay the hyperglycemic action of epinephrine, and (3) delay and diminish the urinary excretion of subcutaneously injected thiamine chloride. The posterior pituitary extract was given to two normal persons in doses of 0.4 I.U. and to three patients with diabetes insipidus in from 8 to 10 I.U. Each individual served as his own control. In the normal following water ingestion under standardized conditions, significant diuresis was delayed for approximately 1½ hours by the injection of the posterior pituitary extract and for approximately three to four hours when such material was combined with zinc. Similar retarding effects were seen in patients with diabetes insipidus. The characteristic action of epinephrine in doses of 1.6 mg. upon the pulse rate, blood pressure and blood sugar of each of four individuals was delayed and prolonged by the addition of the zinc chloride. Urinary excretion of thiamine chloride was studied in seven individuals, four of whom received 10 mg. and three of whom received 50 mg. intramuscularly on a number of test days. As a rule, the rapidity of thiamine excretion and the total amount lost in 24 hours was appreciably diminished by the addition of the zinc chloride, the maximum excretion occurring 1 to 2 hours later and the total amount decreasing from 12 to 63 per cent.—*T.H.McG.*

Ginsburg, G.

Diagnosis of menstrual disturbances by microscopical examination of uterine scrapings. *M. Rec.* 145: 353. 1943.

This paper is a verbal description of the microscopic findings in uterine scrapings from patients with menstrual dysfunction, and of the findings in the normal cycle. Its purpose is to enable the general practitioner to visualize the problem of menstrual dysfunctions more clearly, and to plan treatment more intelligently. It admittedly contains nothing new.—*H.W.*

Lewis, R. M.

Modern methods of procedure in obstetric and gynecologic practice. *South. M. J.* 36: 363. 1943.

This paper is a status report of modern methods in the above field. The author finds that progesterone is not particularly helpful in the treatment of threatened or habitual abortion. Estrogens are of practical value in relieving menopausal discomfort, suppressing lactation, and treating, senite vaginitis. An interesting parallel is drawn between the present results of sex hormone therapy and those obtained in 1908–1918 by the use of glandular preparations which later biologic assay showed to be almost inert. In the author's practice thyroid and posterior pituitary extracts have proved more useful than the sex hormones.—*H.W.*

Pasqualini, R. O., and A. C. Avagadro.

Diuretic action of pitressin after acute nephritis. *Rev. Soc. argent. Biol.* 18: 404–409. 1942.

The antidiuretic effect of pitressin was studied in 19 cases of acute nephritis. In 17 it was considerably reduced owing to a diminished capacity for reabsorption by the tubules. This effect appears early in the disease and is one of the last to disappear in cases with a favorable outcome.—*J.T.L.*

Roffo, A. H., and A. E. Roffo, Jr.

The role of the female sex hormone in precancerous states. *Bol. Inst. med. exp.* 19: 559. 1942.

By spectrographic absorption, blood content of estrogen was determined in young female patients, with and without fibro-adenomatous changes in the breast. In the former there could be demonstrated, both during the menstrual and the intermenstrual periods, an evident increase in

estrogen content. It is believed that any woman showing breast changes should receive, in addition to the usual local treatment, accessory treatment designed to reduce estrogen output to more normal levels.—*Courtesy Biol. Abst.*

WERNER, A. A.

The male climacteric: additional observations on thirty-seven patients. *J. Urol.* 49: 872. 1943.

This paper is a description of the objective signs and subjective symptoms which accompanied hypogonadism in 37 of the author's patients. The symptoms are discussed in some detail. Those occurring in more than 40% of the patients, listed in decreasing frequency, are: subjective nervousness, potency decrease, mental depression, decreased memory and concentration, fatigability and lassitude, loss of interest and self confidence, disturbed sleep, irritability, excitability, fear of impending danger, occipitocervical aching, numbness and tingling, vertigo, hot flushes, headache, and constipation. These patients, 27 of whom were in the male climacteric had a mean age of 53 years; the onset of climacteric symptoms was much later than the onset of menopausal symptoms in a group of women previously reported by the author, who had a mean age of 40.8 years. Résumés of typical cases are given for cryptorchidism, castrate, hypogonadism, climacteric, and involutional melancholia. The paper shows the type of useful data, that can be collected by a clinical endocrinologist without the help of hormonal assays.—*H.W.*

GONADS

CAPONE, A. J.

Ovarian cysts complicating pregnancy. *Am. J. Surg.* 61: 387. 1943.

Three case reports. The presence of an ovarian cyst is not incompatible with normal pregnancy, labor or puerperium. The usual complications occurring in the non-pregnant is more apt to occur in the pregnant. Ovariotomy is indicated in every case of pregnancy complicated by an ovarian cyst. It should not be done during the first three months of pregnancy because of the possibility of removing the corpus luteum and resulting in abortion. If the presence of the cyst is first diagnosed in the last months of pregnancy, one of two courses is indicated: either to wait until full term and then do a cesarean section and ovariotomy, rather than subject the cicatrix of recent operation to the strain of labor; or else, if labor and delivery promise to be uncomplicated, let them occur normally and then do an ovariotomy early in the puerperium. If the diagnosis of cyst is first made in the puerperium, ovariotomy should be performed immediately.—*D.A.M.*

DUNCAN, G. H.

Treatment of prostatic carcinoma by oestradiol and diethylstilbestrol. *Brit. Med. J.* 2: 137. (July 31) 1943.

Three cases of carcinoma of the prostate, all advanced, are reported. Improvement by treatment with large doses of oestradiol benzoate and diethylstilbestrol was marked and sustained. Improvement of metastases appeared to take place with that of the primary growth.—*R.B.G.*

GITLOW, S., AND D. M. KURSCHNER.

Estrogen, diabetes and the menopause. *Arch. Int. Med.* 72: 250. 1943.

The authors' patients were divided into the following 4 groups: (1) those in whom the onset of diabetes coincided with that of the menopause, (2) those in whom existing diabetes was aggravated by the menopause, (3) those in whom the diabetes appeared long after the menopause and (4) 2 who had had no menopausal symptoms but who could not take insulin because of severe local reactions, presumably allergic. Of the 15 patients 8 had a concomitant onset of diabetes and the menopause, 2 had diabetes aggravated by the menopause and in 3 diabetes appeared long after the menopause. The 2 patients whose existing diabetes was aggravated by the onset of menopause demonstrated the effect of estrogen on diabetes aggravated by this phase of pituitary activity in contradistinction to that which has developed some years after the menopause and therefore presumably in the quiescent phase of the anterior lobe of pituitary gland. Patient 13 was intensively studied for several years from the standpoint of concomitant diabetes mellitus and diabetes insipidus. She had extreme polyuria which did not parallel the grade of her glycosuria and which, indeed, antedated her diabetes. When her urine was sugar free and she was still having polyuria, the specific gravity of her urine was much below 1.010, usually 1.002 to 1.004. Control of the polyuria was obtained readily with pitressin, although this would be expected to increase glycosuria and with it polyuria. The patients with concomitant diabetes and the menopause all

responded favorably to estrogen, as well as those with aggravation of diabetes at the time of the menopause. The other 2 patients with onset of diabetes long after the menopause were not thus benefited. The 2 allergic patients, too, showed no response to estrogen therapy. The diagnosis of the menopause was assumed on the basis of subjective complaints, such as headaches, flushes, palpitation, emotional instability, perspiration, vague muscle pain and disturbances of the menstrual rhythm. These findings agree with those of Mazer and Israel that the glycosuria and hyperglycemia can be controlled only by large doses of estrogen. Only 1 patient received 30,000 international units of estrogen weekly. The others required from 60,000 to 80,000. The response to estrogen was the same with estrone (ketohydroxyestrin) and estradiol benzoate (dihydroxyestrin benzoate) provided large doses were given. Improvement in the diabetes closely paralleled that of the menopausal symptoms. Subjective improvement was always accompanied by marked reduction of glycosuria and hyperglycemia. The urine frequently became sugar free. The authors' experience with diethylstilbestrol given by mouth was limited because of the recent introduction of this substance for clinical trial, but if one judges from the scanty available data its effect on hyperglycemia does not parallel its effect on menopausal symptoms. This work with a limited number of subjects indicates that the proper patients for this treatment are those in whom diabetes develops at about the same time as the menopause or those with aggravation of diabetes at this period. Treatment of diabetes with estrogen must not be lightly undertaken. It must be carried out only by physicians with a thorough knowledge of the problems involved, and with careful observation of the patient. It should not be generally undertaken until all the problems concerned with its use have been solved.—*I.B.*

HAIN, A. M.

The control of menopausal flushes by vitamin E. *Brit. Med. J.* 2: 8. (July 3) 1943.

Wheat germ oil was tried for the alleviation of menopausal flushes and headaches because of the experiences of Shute in this connection. In 3 or 4 cases in which it was tried, it appears that some relief was obtained. The author suggests that this mode of therapy be given a trial, especially where idiosyncrasy for estrogens exists.—*R.B.G.*

HUGGINS, C.

Effect of orchiectomy and irradiation on cancer of the prostate. *Ann. Surg.*, 115: 1192. 1942.

In a series of 45 consecutive patients with advanced prostatic cancer, the primary treatment was bilateral orchiectomy. In 31 cases a sustained inhibition of the disease occurred, lasting at least as long as 30 months; in nine patients there was temporary improvement and in 5 men, castration caused no clinical improvement. There were 8 deaths, all in men with metastasis to bone; in four of these, carcinomatosis was the principal cause of death. In these four cases, and likewise in those patients who showed little or no improvement following orchiectomy, the tumor was undifferentiated carcinoma. In the cases in which the results of the operation were more satisfactory, the tumor was adenocarcinoma. A great decrease in the size of the primary neoplasm, while the metastases were advancing, was observed in five cases. Ten of the patients whose response to orchiectomy was unsatisfactory were given diethylstilbestrol, 1–3 mgm. daily by mouth; there was no indication that this treatment was useful as a supplementary measure. In two cases, roentgenotherapy was applied to the pelvis and testes prior to orchiectomy. Roentgen irradiation produced atrophy of the germinal epithelium but not of the interstitial cells of the testis and was inadequate as a therapeutic measure. Three of the patients who died of carcinomatosis had testes which, considered singly, weighed 8–10 gms. at operation. Severe hot flashes were a feature of all of the cases favorably influenced by orchiectomy. In the author's opinion, these vasomotor incidents are usually of favorable prognostic importance.—*D.P.*

MOORE, R. A., AND M. L. MILLER.

The ratio of urinary androgen and estrogen in relation to benign hypertrophy of the prostate. *J. Urol.* 49: 861. 1943.

This is an intensive study of androgen and estrogen excretion from two senile males for a period of one month. One of these males, (P), had an enlarged prostate, that of the other, (B), was described as "normal." For the month, P had a mean estrogen/androgen ratio of .61; B had a mean ratio of .19. The mean androgen excretion of both patients was approximately the same; the difference in the ratios is due largely to an in-

creased estrogen excretion by P. No tests of significance were applied to these differences, although the variance of the daily excretions is large. This is admittedly a preliminary paper; the authors hope that further research will show that in patients with benign hypertrophy of the prostate, there is in the urine a higher estrogen/androgen ratio. At present such extrapolation is unwarranted.—*H.W.*

ROBIE, T. R.

Psycho-endocrinotherapy in personality disorders of eunuchoidism. *Dis. Nerv. System* 4: 42. 1943.

Testosterone in propylene glycol administered sublingually at regular intervals was sufficient to maintain potency established by parenteral therapy. A male, 33, who had been impotent during 6 years of marriage, was given parenteral injections of testosterone propionate. After 6 months the intramuscular injections were gradually reduced and supplemented by methyl testosterone tablets given orally. A few weeks later these were replaced by testosterone in propylene glycol. Potency has remained normal for over a year. Apparently methyl testosterone tablets or testosterone in propylene glycol are equally effective in maintaining potency established by parenteral therapy.—*Courtesy Biol. Absts.*

STORCK, A. H., AND J. SABATIER.

The use of estrogenic substances in the pre- and postoperative treatment of hyperthyroidism. *Ann. Surg.* 115: 821. 1942.

Therapy with estrogenic substances was employed in 11 cases with hyperthyroidism having an average basal metabolic rate of plus 47.7 per cent, four of which were iodine-fast and four of which manifested such toxicity that multiple-stage operations were deemed advisable. The response to preoperative treatment and operation of the estrogen treated patients was compared with corresponding observations made in 11 cases of hyperthyroidism in which estrogenic therapy was not employed. The patients who received estrogen therapy consistently looked and felt better than did the control group, the difference being most pronounced during the immediate postoperative period. An average preoperative lowering of pulse rate equal to that which occurred in the control group was observed in the estrogen treated patients. The average peak pulse rate of the first postoperative day was lower in the group receiving estrogen therapy than in the control group. No crises occurred in the estrogen treated group. Comparison of patients with toxic diffuse goiters and those with toxic nodular goiters revealed no significant difference in the response to estrogen therapy. The rationale for the employment of estrogen therapy on hyperthyroidism was discussed and it was pointed out that the observations reported imply that such therapy is valuable only as an adjunct in the surgical treatment of hyperthyroidism. The authors believe that the employment of this form of collateral therapy is warranted, especially in a) severe cases of hyperthyroidism, particularly when multiple stage procedures are necessary and b) in iodine fast cases. Theelin and diethylstilbestrol were employed in the study but no conclusions could be drawn concerning the relative values of the two preparations as estrogenic substances suitable for use in hyperthyroidism. Likewise no conclusions could be drawn concerning a relation between dosage and effect. Observations on this point suggested that small doses of estrogenic substances are as effective as large doses, if not more so. Estrogen therapy seemed to be most effective when administered for from 4 to 7 days preceding operation when subtotal thyroidectomy was undertaken in one stage. In the case of multiple-stage thyroidectomy, the authors recommend that estrogen therapy be continued for several days following the first stage and reinstituted preceding the second stage, especially if there is a lapse of more than a week between operations.—*D.P.*

THIESSEN, N. W.

Polyorchidism—report of a case. *J. Urol.* 49: 710. 1943.

Since 1670, 13 cases of histologically proven polyorchidism have been reported in the literature. The case reported here was discovered at an Army hospital. The patient was found to have an atrophic right testis, a normal left testis, and an abdominal testis. There were both scrotal and abdominal epididymides. The abdominal testis and epididymis were found to be normal, although there were no signs of spermatogenesis. The smaller scrotal testis was also atrophic, with no spermatogenesis. This is believed to be the first reported case with an apparent complete reduplication of all structures.—*H.W.*

HYPOPHYSIS

COURT, D., AND S. TAYLOR.

Slowly acting pituitary preparations in diabetes insipidus. *Lancet* 1: 265. (Feb. 27) 1943.

Pitressin tannate in oil seems to be the safest and most effective slowly acting preparation of the posterior pituitary lobe so far available for the treatment of diabetes insipidus. Pituitary emulsion, though giving excellent control, has several drawbacks, notably the delayed formation of paraffinomata at the injection sites. Four cases of diabetes insipidus showing the effects of these two preparations are reported.—*R.B.G.*

COURT, D., AND S. TAYLOR.

Slowly acting pituitary preparations in diabetes insipidus. *Lancet* 244: 265–267. 1943.

Pitressin tannate in peanut oil and pituitary emulsions in woolfat, beeswax, p-chlorometaxylenol and olive oil mixture were administered to 4 patients. Both preparations are effective, but the former is preferred since delayed paraffinomata may occur at the sites of injection of the emulsion.—*Courtesy Biol. Absts.*

PANCREAS

DUBOVSKY, B.

Diabetes mellitus. *M. Rec.* 156: 358. 1943.

The author considers the symptom triad hyperglycemia, glycosuria, and reduction in sugar tolerance not as the disease entity, diabetes mellitus, but as a symptom complex found in a variety of bodily disorders. When this diabetic triad occurs in patients at about the sixth decade of life it is indicative of a lowering of all bodily functions, including that of metabolizing food. When it is found in women at 40 to 50 years of age, the etiological factor may be an overactivity of the anterior pituitary, initiated by menopausal ovarian failure. This statement is supported by several literature references showing that the anterior pituitary influences carbohydrate metabolism; that castration causes increased gonadotropic hormone excretion, and that some of the hormones of the anterior pituitary are inter-related. The author's other two groups are adults between the ages of 20 and 40, who have inherited a potentially weak body mechanism, and children, in whom alone he assumes that diabetes is an inherited disorder of metabolism. The author suggests that the number of diabetics would be markedly decreased by the elimination of those for whose symptoms an assignable cause can be found, and our attention could be concentrated on those cases in which the causes for the diabetic triad are not so easily rationalized.—*H.W.*

DUNN, J. S., H. L. SHEEHAN, AND N. G. B. MCLETCHIE.

Necrosis of islets of Langerhans. Produced experimentally. *Lancet* 1: 484. (Apr. 17) 1943.

Acute necrosis of almost all the islet tissue of the pancreas has been observed in rabbits after intra-peritoneal inoculation of a synthetic styrylquinoline, and also after intravenous inoculation of alloxan. The development of this lesion is accompanied by an initial rise of blood sugar, followed by an intense hypoglycemia which ends fatally with subnormal temperature in 12–48 hours. It is suggested that the lesion may be caused by overstimulation of the islets with overproduction of insulin, and later death of the cells from overstrain. The mechanism of production of the lesion is discussed and reference is made to the possible role of alloxan as a hormone of muscle. Investigation of this lesion is suggested as one line of inquiry into the causation of diabetes mellitus.—*R.B.G.*

HARRIS, M. M.

Effect of insulin hypoglycemia and glucose administration on the level of the glutamine-like substance in blood serum. *J. Clin. Invest.*, 22: 577. 1943.

Following the administration of insulin in a sufficient dose (25 to 175 units) to produce hypoglycemia in each of seven subjects suffering from mental disease, there was an appreciable diminution of a glutamine-like substance in the blood. This decrease was not favorably influenced by the administration of glucose in sufficient quantity to relieve the hypoglycemia completely. On the contrary, in each of two mentally sick individuals, glucose alone (75 grams administered in the post-absorptive state) caused a reduction in the blood level of the glutamine-like substance. The findings are brought into positive relationship with the inhibitory action of insulin on oxidative deamination.—*T.H.McG.*

HOLMAN, E., D. A. WOOD, AND A. B. STOCKTON.

Unusual cases of hyperinsulinism and hypoglycemia. *Arch. Surg.* 47: 165. 1943.

1. Recorded in the literature are four cases of extra-pancreatic islet adenomas producing symptoms of hyperinsulinism and hypoglycemia which were entirely controlled by removal of the extrapancreatic adenoma. To these four is added a fifth case in which removal of one intrapancreatic adenoma failed to relieve the hypoglycemic symptoms, but in which the removal of a second islet adenoma in the gastrosplenic ligament produced complete cure. In any operation undertaken in a case in which Whipple's triad of hypoglycemic symptoms is present, the possibility of multiple adenomas must be borne in mind as well as the possibility of an islet tumor lying in extrapancreatic tissue. Failure to find an intrapancreatic tumor should be followed by careful search for an islet tumor in those sites where heterotropic pancreatic tissue is frequently found. 2. Reported also is a case of heterotropic islet adenoma of the duodenum without hypoglycemic symptoms. 3. A case of islet carcinoma apparently engrafted on a calcified islet adenoma which presumably had been responsible for hypoglycemia of varying severity over a period of 16 years if presented. 4. A bizarre case of hypoglycemia characterized by episodes of unconsciousness and blood sugar values as low as 33 mgm. per 100 cc. is reported. The patient's abdomen was explored for an islet adenoma but none was found. In the course of the operation the pancreas was isolated from all surrounding structures, although its arterial supply was not interrupted. No evidences of hypoglycemia have ever again appeared. No explanation for this astonishing and unexpected result is offered.—*Authors' Summary.*

INGALLS, T. H., G. DONALDSON, AND F. ALBRIGHT.

The locus of action of the parathyroid hormone: experimental studies with parathyroid extract on normal and nephrectomized rats. *J. Clin. Invest.* 22: 603. 1943.

Growing rats were divided into four groups: nephrectomized and injected with parathyroid extract (200 units); nephrectomized, uninjected; normal, injected; and normal, uninjected. Two groups of experiments paralleled each other save that in the first the animals were sacrificed at 60 hours and in the second at 20 hours. In both the normal and nephrectomized animals receiving parathyroid extract there was always a characteristic osteitis fibrosa in the metaphyses of the long bones which was "characterized by a relatively complete resorption of the primary spongiosa" and replacement by a "fibrous, soft tissue composed of osteoblasts, foreign body giant cells (osteoclasts), and exudate." In nephrectomized uninjected rats, sacrificed at the end of 60 hours, a different type of metaphyseal rarefaction occurred, which differed from that just described in the following way: 1) decalcification occurred more distally, i.e., farther from the epiphyseal cartilage; 2) the zone of provisional calcification was less demineralized than in animals receiving the extract; 3) normal organization of tissue structure was less disturbed; 4) fibrous tissue was less; and 5) no exudate was present. In general, decalcification was less extensive than that following injection of the extract. In the nephrectomized uninjected animals, sacrificed at the end of 20 hours, none of these changes, which the authors speak of as "renal rickets," had occurred. A third group of experiments proved that the acidity of the parathyroid extract injected had nothing to do with the bony changes observed as a result of their administration. The authors conclude that parathyroid extract produces a characteristic osteitis fibrosa which is qualitatively and quantitatively different from that due to nephrectomy alone.—*T.H.McG.*